ARCALYST® (rilonacept)

United States Food and Drug Administration Arthritis Advisory Committee Meeting

REGENERON

Introduction

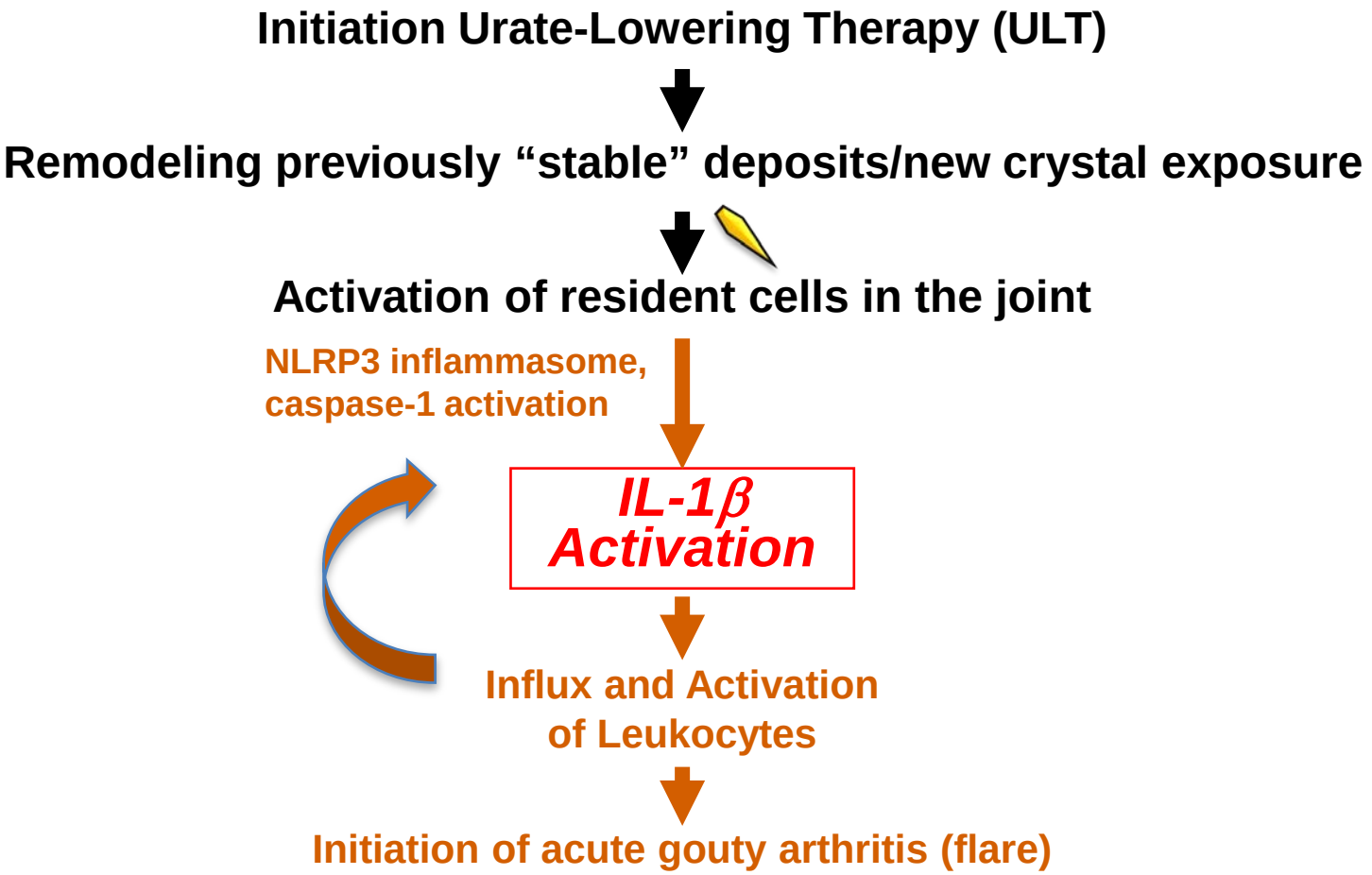
George D. Yancopoulos, MD, PhD

Chief Scientific Officer
Regeneron Pharmaceuticals

ARCALYST® (rilonacept)

- **Currently approved indication (from 2008):**
  - **ARCALYST® (rilonacept)** is an **interleukin-1 blocker** indicated for the treatment of **Cryopyrin-Associated Periodic Syndromes (CAPS)**, including Familial Cold Auto-inflammatory Syndrome (FCAS) and Muckle-Wells Syndrome (MWS), in adults and children 12 and older.
- **Clinical experience: Favorable safety and efficacy profile**
  - ~100 patients treated for 1 to 2 years in clinical trials
  - ~80 patients during marketed treatment for up to 4 years

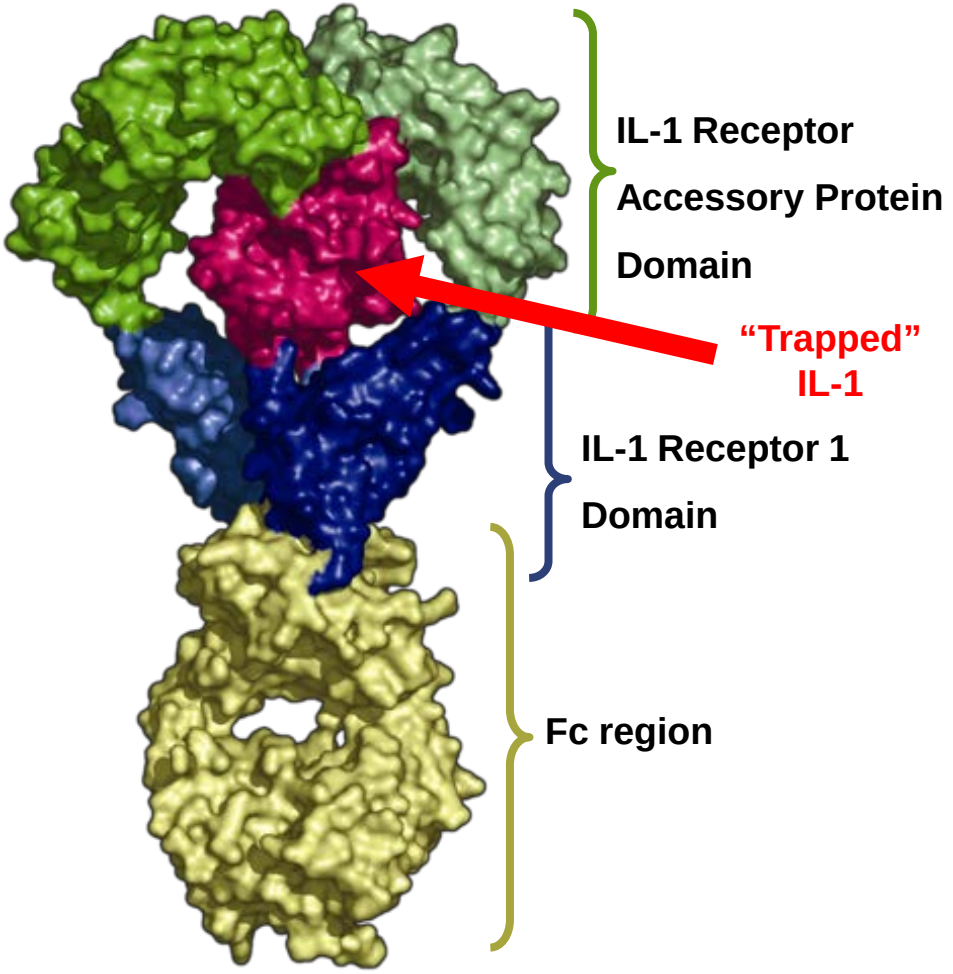
Paradoxically, Initiation of Urate-Lowering Therapy (ULT) "Triggers" Acute Gouty Flares



Adapted From: Gout and Other Crystal Arthropathies, Terkeltaub R (ed), Elsevier, 2011.

Rilonacept (Interleukin-1 Trap): Binds and Blocks IL-1

- Soluble Decoy Receptor
- Entirely Human Components:
  - IL-1 receptor binding domains fused to Fc region of human IgG1
- Half-life ~ 1 week



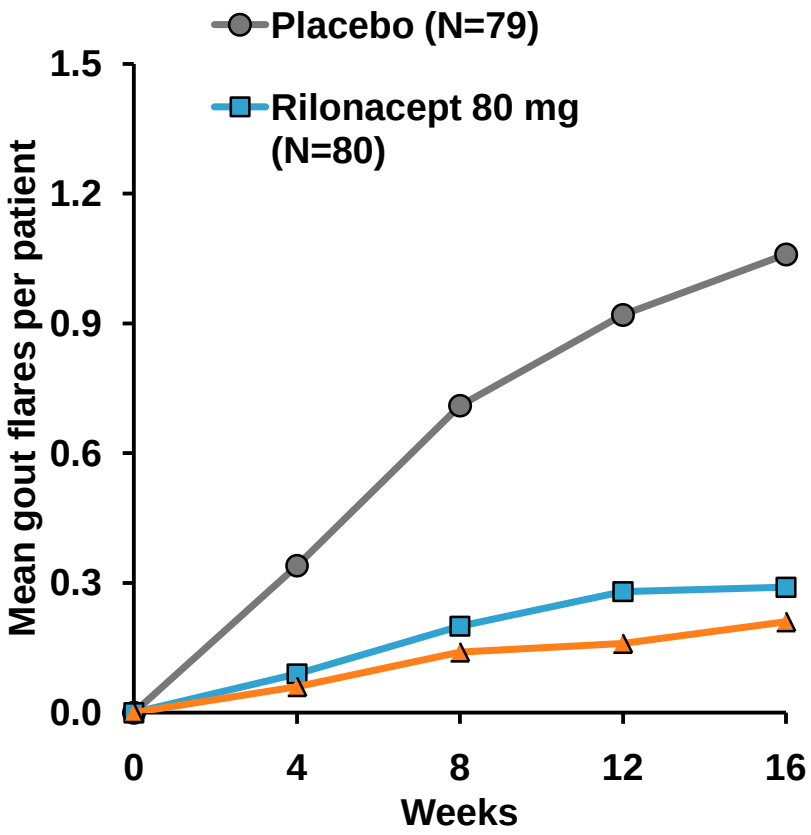
Rilonacept Clinical Development Program for Prevention of Gout Flares

- First comprehensive clinical development program for gout prophylaxis indication
- Two placebo-controlled Phase 3 Efficacy studies and a large placebo-controlled Phase 3 Safety study that also assessed efficacy
  - Weekly doses of both 80 mg and 160 mg evaluated
- Design of Phase 3 studies for prophylaxis indication incorporated advice provided by FDA at End-of-Phase 2 meeting
- Overall program evaluated more than 1800 gout patients, including more than 1350 treated with rilonacept, including about 1000 treated for 16 weeks, our proposed duration of therapy

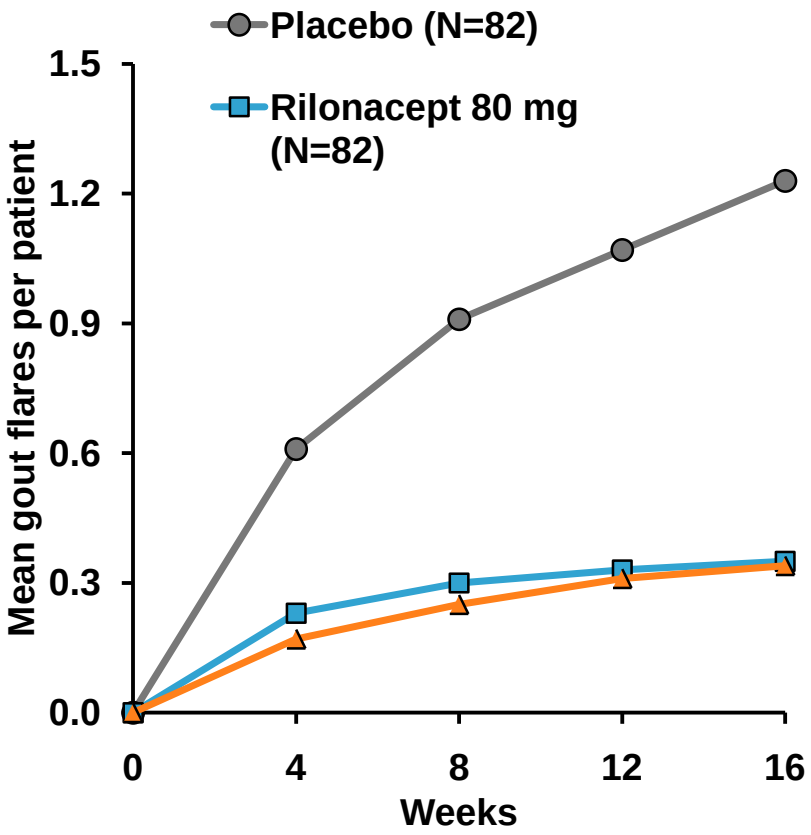
Rilonacept Efficacy Summary: 70-80% Reduction in Gout Flares

Phase 3 Efficacy Studies 0810 and 0816

Study 0810



Study 0816



- Similar decreases across all subgroups of interest

0810 CSR Table 11.1.1; 0816 CSR Table 11.1.1

Rilonacept Safety Summary

- No impact on infections, serious infections, uric acid reduction, renal function
- Small numeric imbalance in neoplasms well within expected statistical variation
- Safety and tolerability data are very reassuring, with no major safety signals identified

- Limited controlled data to characterize currently approved therapy (colchicine)
  - No controlled data quantifying risk of infections, malignancy, or other less common events
  - Complex drug-drug interactions, associated with fatalities

Proposed Indication

- **ARCALYST® (rilonacept) is an interleukin-1 blocker indicated for the prevention of gout flares during initiation of uric acid-lowering therapy in adult patients with gout.**

  ARCALYST has not been studied for longer than 16 weeks in this clinical setting.

- **Recommended dosing regimen: 80 mg SC weekly after 160 mg SC loading dose.**

Agenda

Introduction	**George D. Yancopoulos, MD, PhD** **Chief Scientific Officer** **Regeneron Pharmaceuticals**
Gout: Disease Awareness and Unmet Medical Need	**Michael A. Becker, MD** **Professor Emeritus of Medicine** **University of Chicago Pritzker School of Medicine**
Clinical Development and Efficacy	**Steven P. Weinstein, MD, PhD** **Therapeutic Area Head, Immunology & Inflammation** **Regeneron Pharmaceuticals**
Safety and Risk Management	**Ned Braunstein, MD** **Head Regulatory Affairs** **Regeneron Pharmaceuticals**
Clinical Perspective	**N. Lawrence Edwards, MD** **Professor of Medicine** **Vice Chairman, Department of Medicine** **University of Florida, Gainesville**

Consultants

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Professor of Medicine
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Lebanon, NH

Charles G. Drake, MD, PhD
Associate Professor of Oncology, Urology, and Immunology
Co-Director Prostate Cancer Multi-Disciplinary Clinic
Sidney Kimmel Comprehensive Cancer Center
John Hopkins Hospital
Baltimore, MD

Disease Awareness and Unmet Need

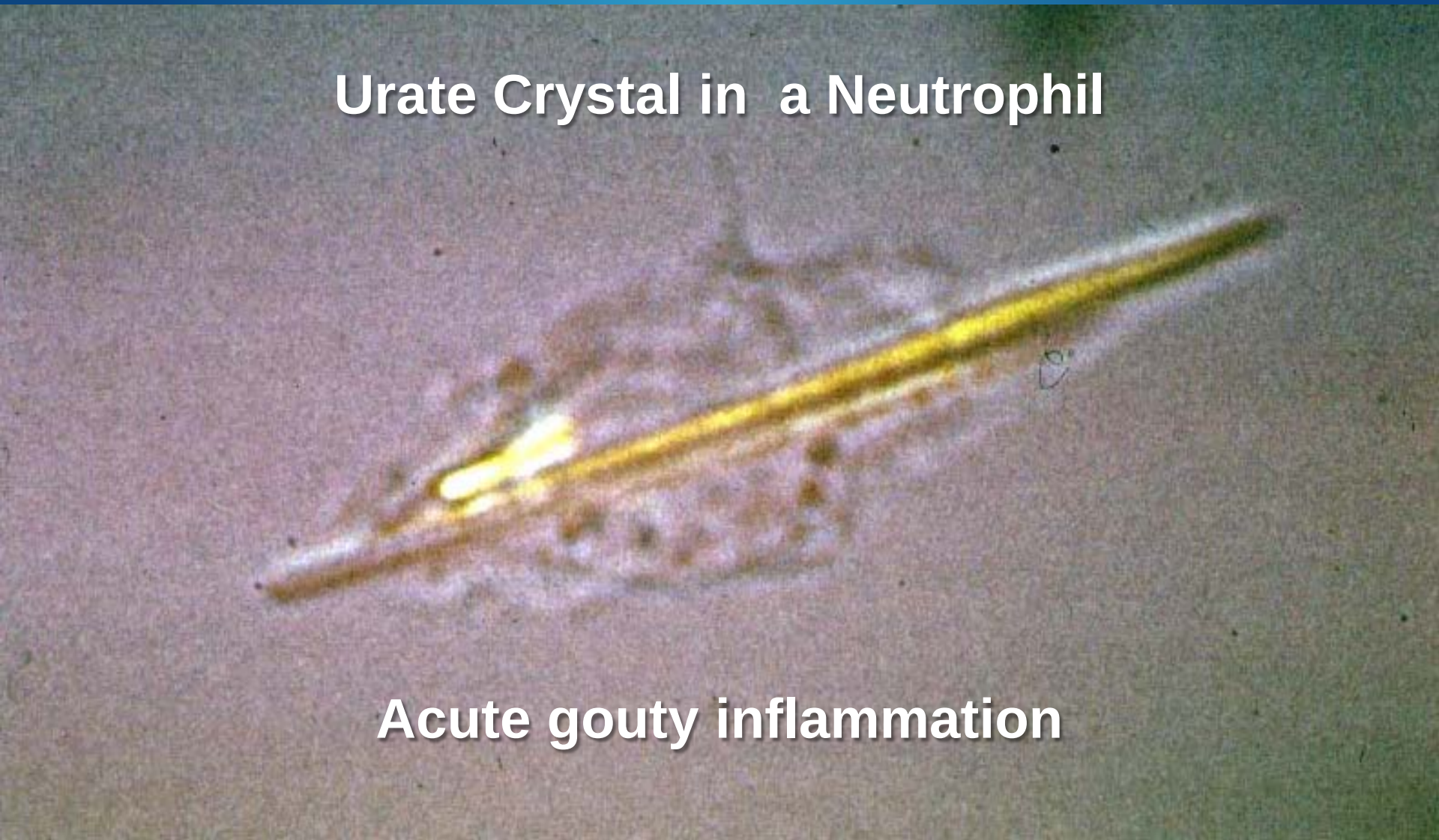
Michael A. Becker, MD

Professor Emeritus of Medicine
University of Chicago Pritzker School of Medicine
Chicago, IL

For disclosure, I am a paid consultant to the sponsor and I have no financial interest in the outcome of this meeting.

Definitions

- Uric acid: end product of human purine metabolism
- Hyperuricemia: serum urate >6.8 mg/dL
  - Common; necessary but not sufficient for gout without urate crystal deposition and an inflammatory response
    - Most often due to impaired renal uric acid clearance (85% to 90%)
    - Increasing hyperuricemia associated with increasing gout risk
- Gout: urate crystal deposition disease


Urate Crystal in a Neutrophil
Acute gouty inflammation

Evolving History of Hyperuricemia and Gout

Asymptomatic hyperuricemia >6.8 mg/dL

Gout

Estimated number of affected persons in the US

15-43 million[a]

- **Often persists over lifetime**
- **Progression to gout: 20%-30%**
- **Strong association with co-morbid disorders**

Management:
Life-style measures

6-8 million[a]

- Acute gouty arthritis

~80% frequent flares

Gout flares

Rare attacks (20% of patients)

Life style measures; anti-inflammatory drugs, as needed

~5-6 million[b]

Long-term urate-lowering agent indicated

- Renal function
- Tophi and functional status
- Stone disease history
- Other comorbidities
- Uric acid production

Goal urate maintained (sUA <6.0 mg/dL) (~50%)
Gout symptom remission in 1- 3 yrs

~2 million

- Persistent or progressive gout
- Arthropathy and tophi

0.2-0.5 million[c]

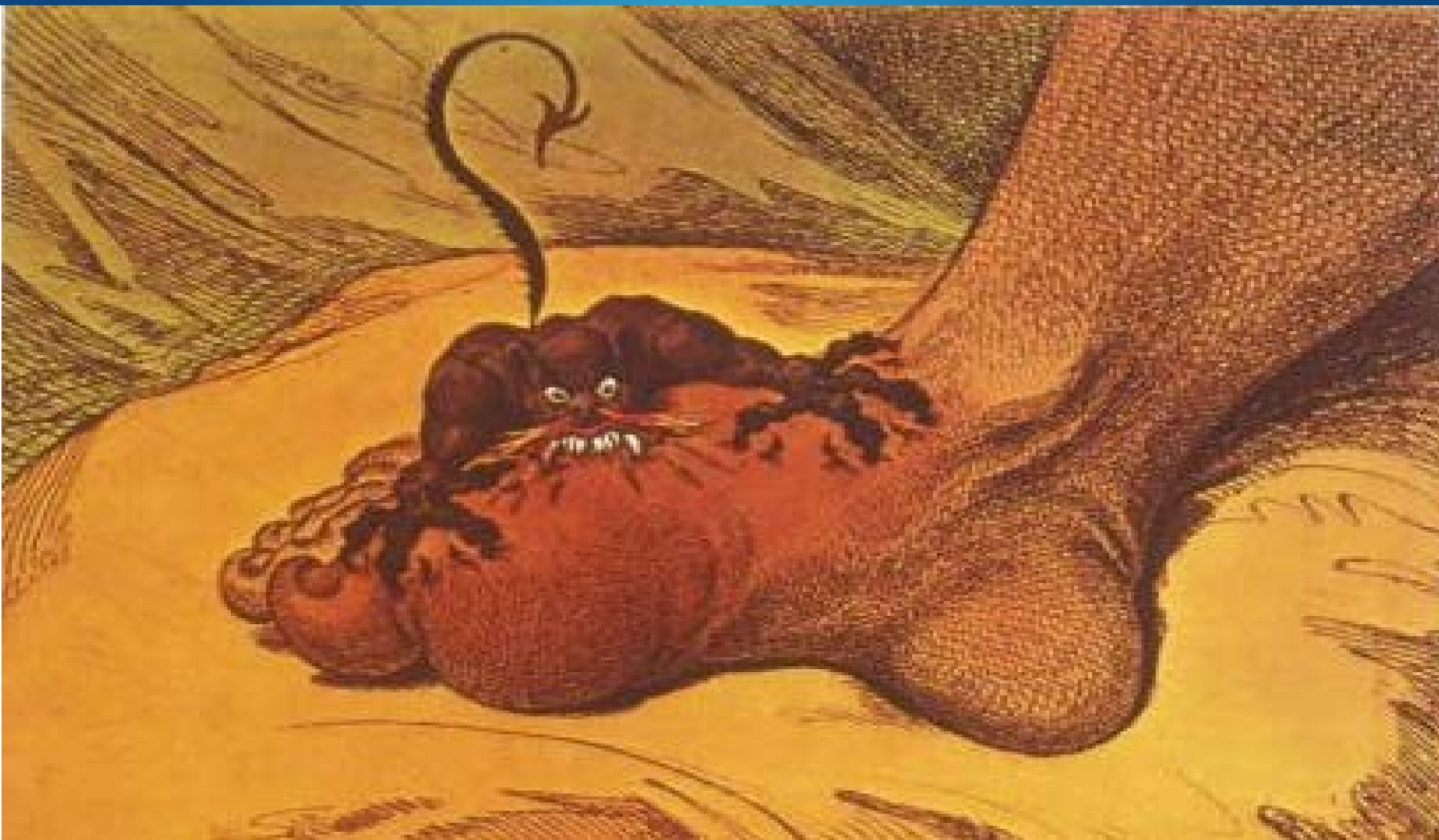
- Worsening arthropathy, enlarging tophi, chronic pain, impaired function and HRQOL

Significant Co-morbidities Frequently Accompany Hyperuricemia and Gout

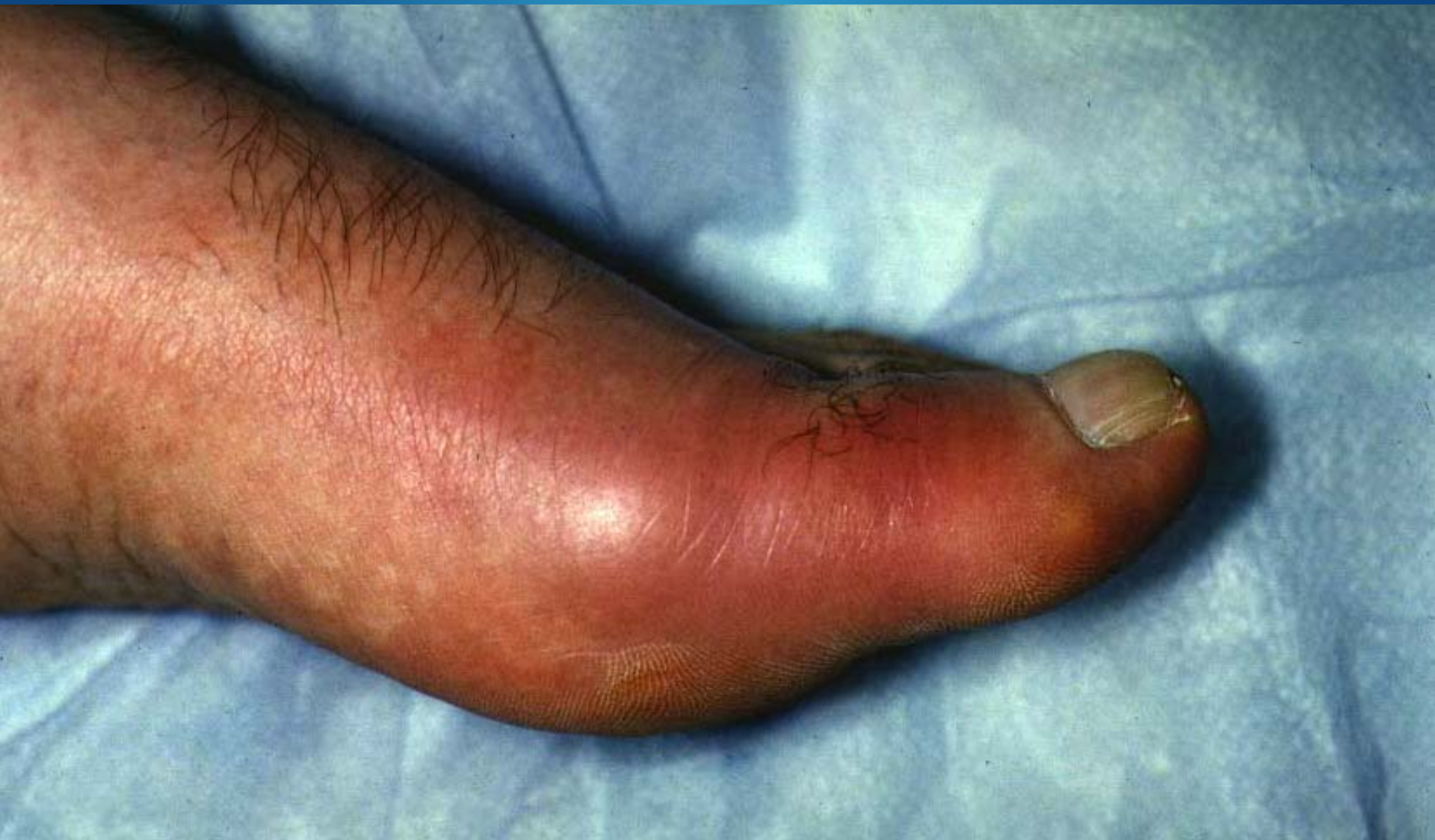
- Hypertension[a]
- Metabolic syndrome[b]
  - Hyperlipidemia[c]
  - Obesity[c]
  - Diabetes mellitus[d]
- Cardiovascular disease[e]
  - Myocardial infarction
  - Stroke
  - Peripheral artery disease
  - Congestive heart failure[f]
- Impaired renal function[g]

[a] Gavin et al. *Am J Cardiovasc Drugs*. 2003;3:309; [b] Ford et al. *JAMA.* 2002;287:356.
[c] Nakanishi et al. *Int J Epidemiol*. 1999;28:888; [d] Boyko et al. *Diabetes Care.* 2000;23:1242.
[e] Niskanen et al. *Arch Intern Med.* 2004;164:1546; [f] Anker et al. *Circulation.* 2003;107:1991.
[g] Vazquez-Mellado et al. *Best Practice Res Clin Rheumatol.* 2004;18:111.

The Gout—James Gillray, 1799



Acute Gouty Arthritis



Gout Flare: a Classical and a US Veteran's Descriptions

"…The night is passed in torture, sleeplessness, turning of the part affected, and perpetual change of posture…"

Sir Thomas Sydenham, 1683

"I've been shot, beat up, stabbed and thrown out of a helicopter, but none of that compared to the gout."

Patient of Kenneth Saag, MD
March, 2001

Evolving History of Hyperuricemia and Gout

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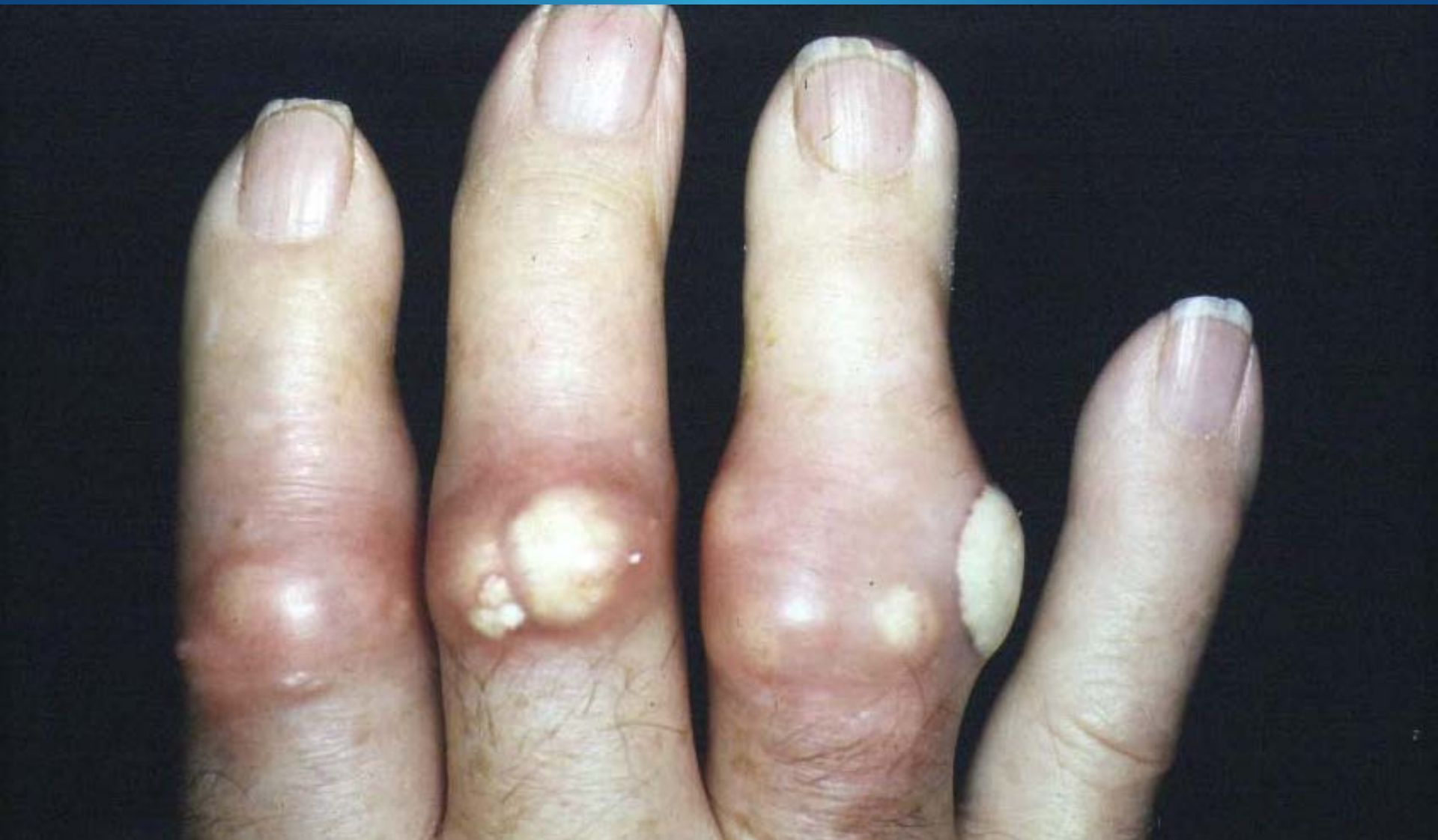
- Persistent or progressive gout
- Arthropathy and tophi

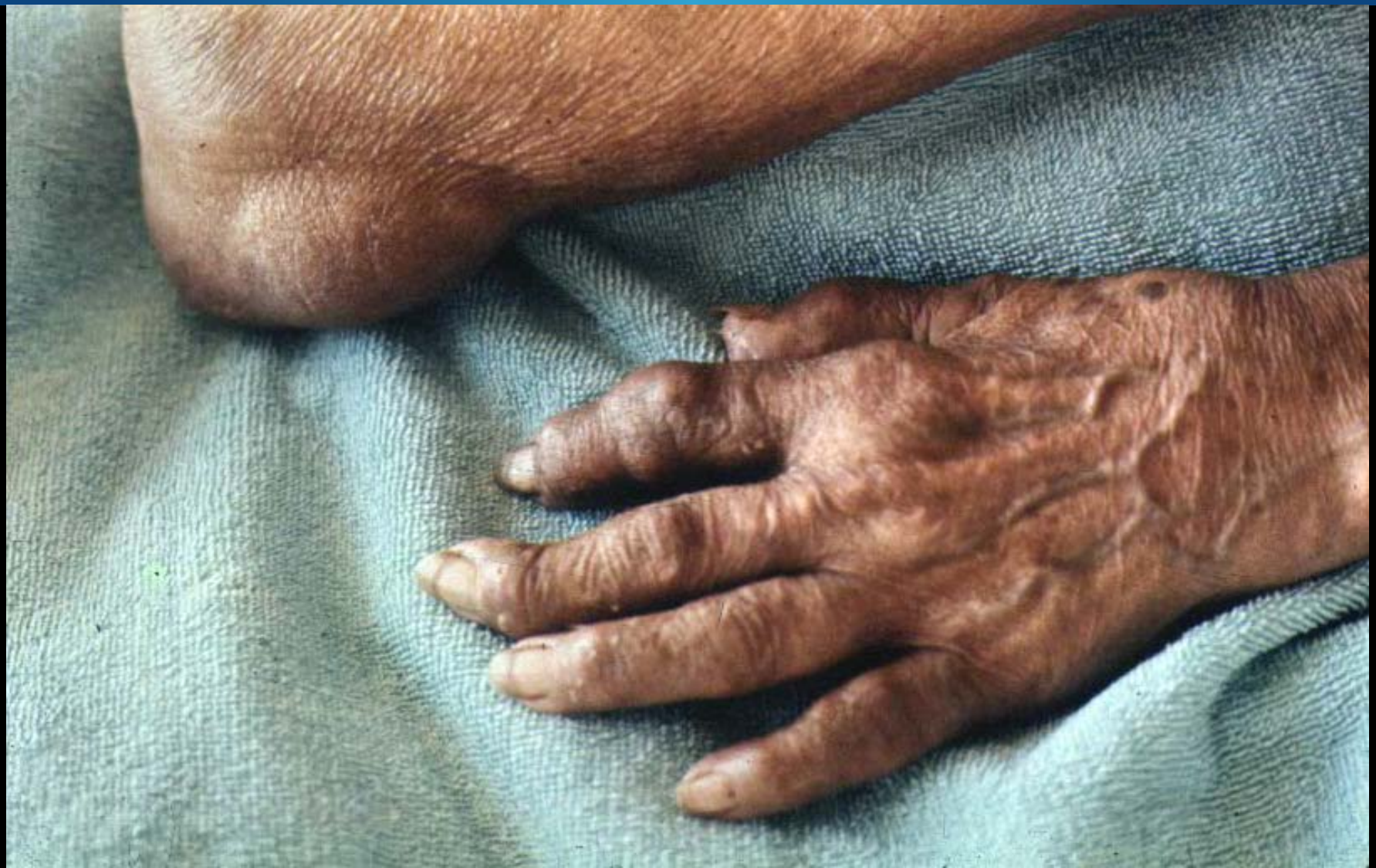
0.2-0.5 million[c]

- Worsening arthropathy, enlarging tophi, chronic pain, impaired function and HRQOL

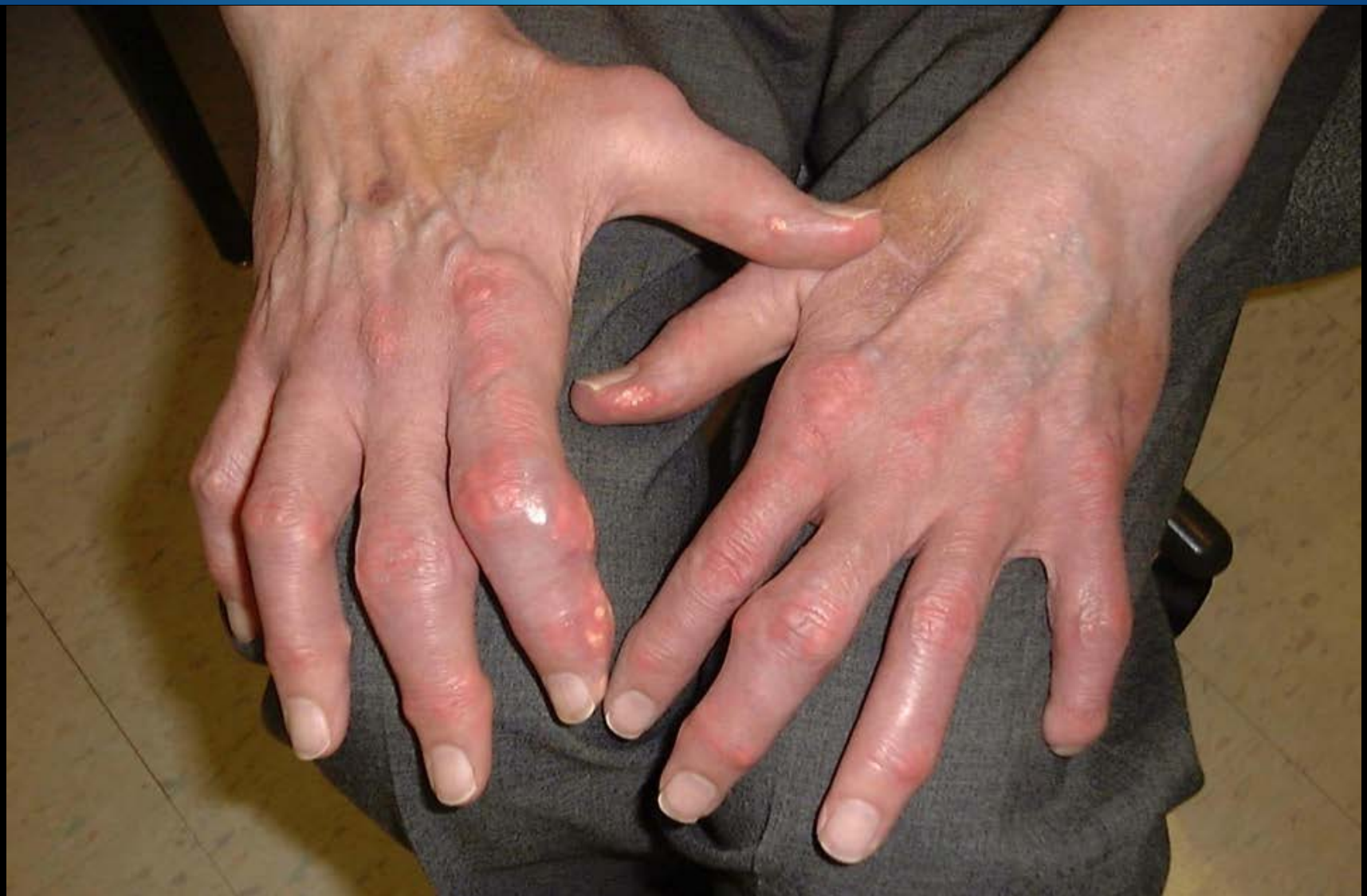
Acute Flare/Chronic Tophaceous Gout



Tophaceous Gout and Chronic Gouty Arthropathy



Chronic Gouty Arthropathy



Gout Affects Patient Quality of Life, Healthcare Utilization and Costs, and Workplace Productivity

- Norm-based SF-36 PCS[a-c] and MCS[b] scores reduced in gout patients
  - Especially those with more frequent flares ($p<0.005$), more affected joints[a,b] ($p<0.001$) and/or co-morbidities[b]
  - These deficits are largely reversible[c]
- All cause annual healthcare costs: gout patients, $14.8K vs controls, $9.3K[d]
- Gout patients cost employers nearly double those of non-gouty employees[e], with mean of 4.6 more days of absenteeism[f]

[a] Lee et al. *Rheumatology*. 2009;48:582-586; [b] Khanna et al. *Rheumatology*. 2011;50:740-745;
[c] Sundy et al. *JAMA*. 2011;306:711-720; [d] Wu et al. *J Manag Care Pharm*. 2008;14:164-175;
[e] Brook RA, et al. *Curr Med Res Opin.* 2006;22:1381-1389; [f] Kleinman NL, et al. *Value in Health.* 2007;10:231-237.

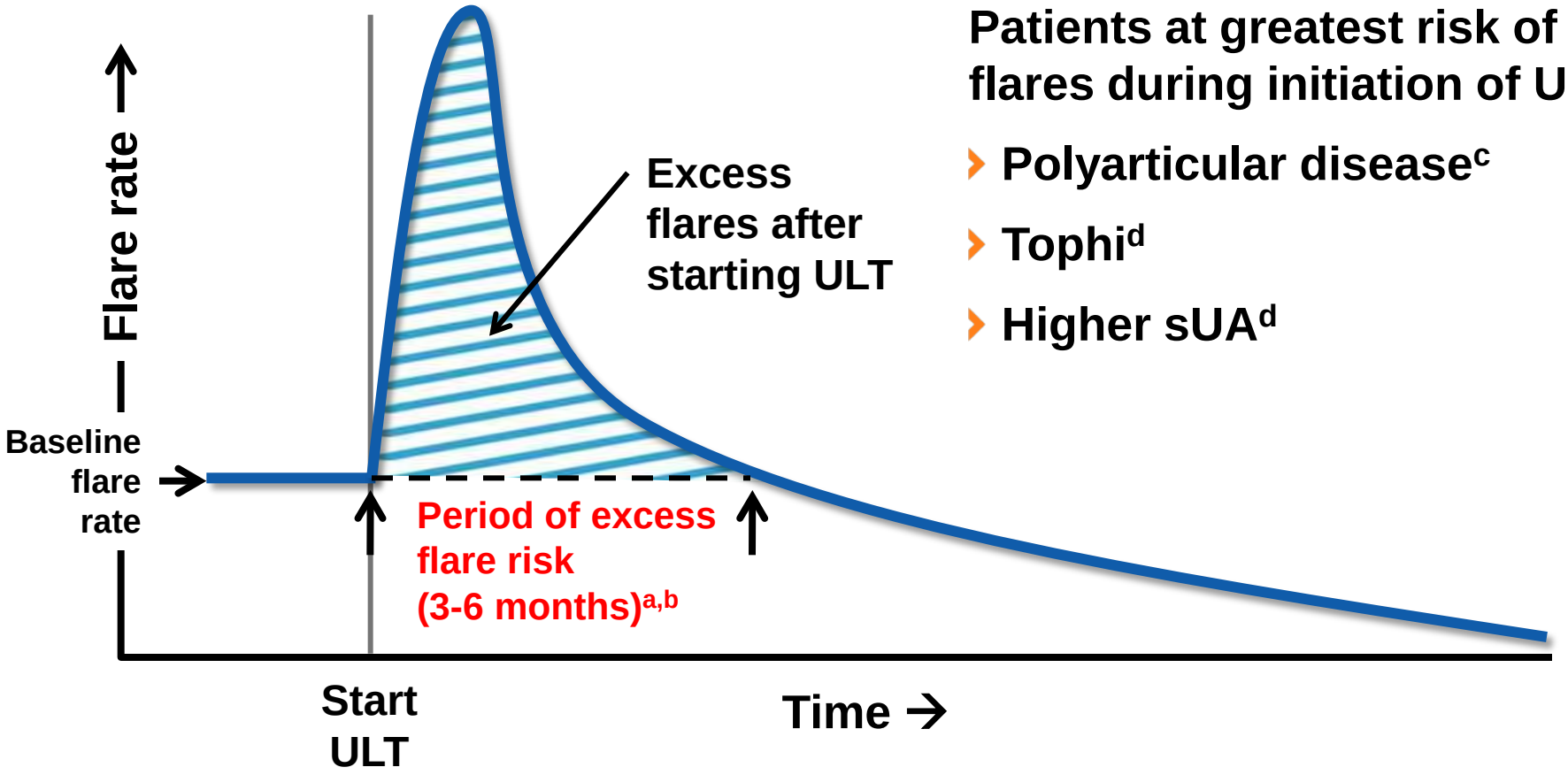
Aims in the Management of Gout

- Prevent the disease
- Terminate pain and disability of acute attacks
- Protect against further attacks during initiation of urate-lowering therapy
  - Anti-inflammatory prophylaxis
- Long-term urate-lowering to <6.0 mg/dL to prevent future attacks and reverse prior damage
- Assess and manage co-morbidities

Aims in the Management of Gout

- Prevent the disease
- Terminate pain and disability of acute attacks
- Protect against further attacks during initiation of urate-lowering therapy
  - Anti-inflammatory prophylaxis
- Lower and maintain serum urate at <6.0 mg/dL
- Assess and manage co-morbidities

Gout Flares Increase During Initiation of Urate-Lowering Therapy (ULT)

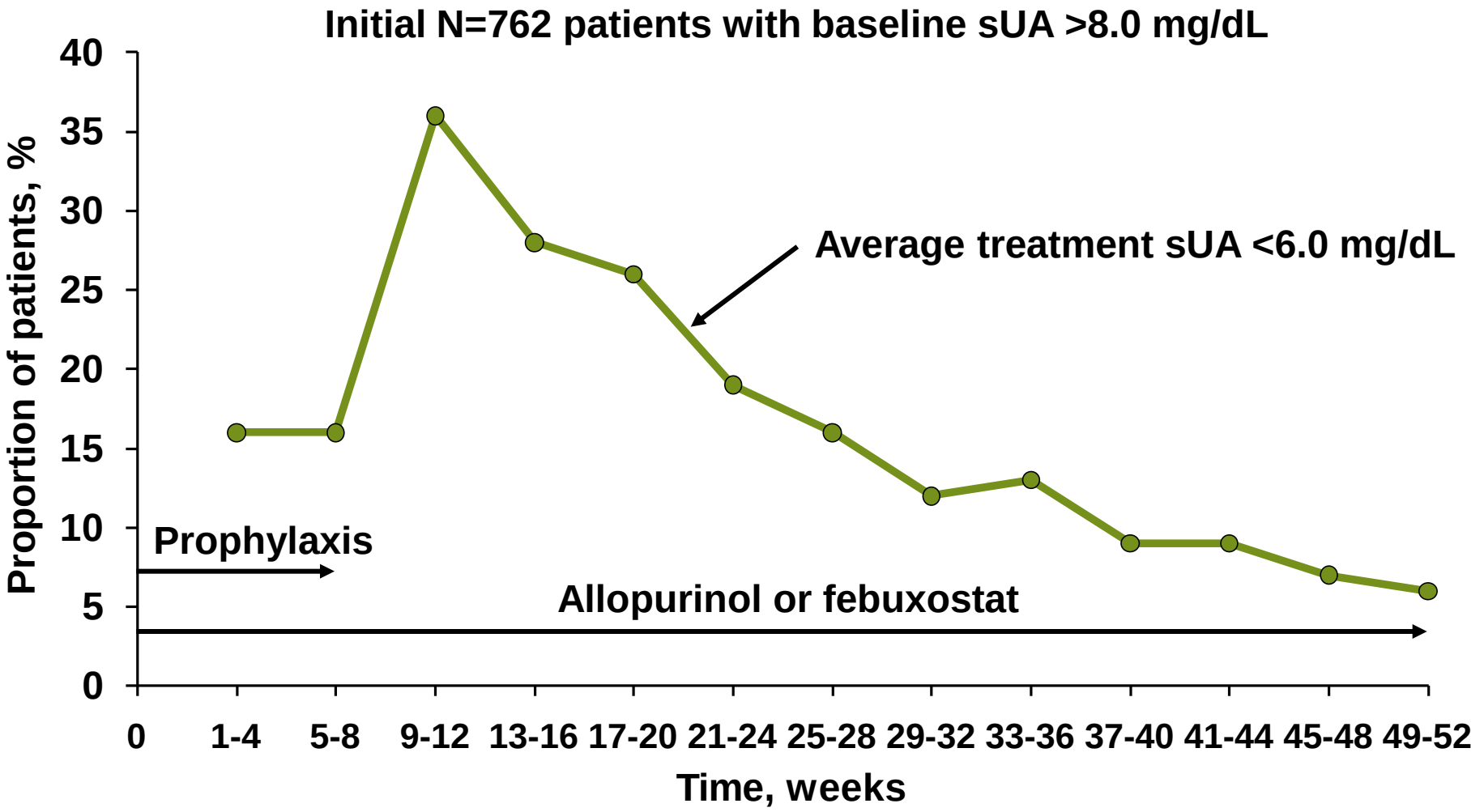


Patients at greatest risk of flares during initiation of ULT

- Polyarticular disease[c]
- Tophi[d]
- Higher sUA[d]

[a] Becker et al. *Arthritis Res Therapy*. 2010;12R63; [b] Sundy et al. *JAMA*. 2011; 306:711; [c] Terkeltaub et al. *Arthritis Rheum*. 2011;10:S395; [d] Becker et al. *Nucleosides Nucleotides Nucl Acids*. 2008;27:585-591.

Gout Flares Transiently Increase During Initiation of Urate-Lowering Therapy (ULT)



Becker MA, et al. *N Engl J Med*. 2005;353:2450-2461.

Increased Flares in Early Months of Urate-Lowering Therapy (ULT) Reduce Adherence

- In a prospective study of ULT, gout flares were associated with premature withdrawal (4.9% for febuxostat 80 mg; 0% for placebo)[a]
- Large retrospective claims analysis, median length of allopurinol treatment for patients with diagnosis of gout was only 3 months[b]
- Majority of patients discontinue ULT during the first year[c]

[a] Schumacher, et al. Arthritis Rheum 2008;59:1540-1548.
[b] Sarawate, et al. *Mayo Clin Proc*. 2006;81:925-934.
[c] Harold, et al. *Arthritis Res Therapy*. 2009;11:R46.

Anti-inflammatory Flare Prophylaxis is Recommended When Starting Urate-Lowering Therapy

- Same medications as used to treat acute flares
  - Colchicine
    - Colcrys approval in prophylaxis based on historical efficacy data using unbranded colchicines (2 RCTs; total N=84 subjects[a,b])
    - Safety database limited with regard to toxicity
  - NSAIDs
    - Commonly used but no high level trial data
  - Corticosteroids
    - No established basis for use

[a] Paulus et al. *Arthritis Rheum*. 1974;17:609.
[b] Borstad et al. *J Rheumatol*. 2004;31:2429.

Safety Limitations of Medications Currently Used for Flare Prevention

Colchicine

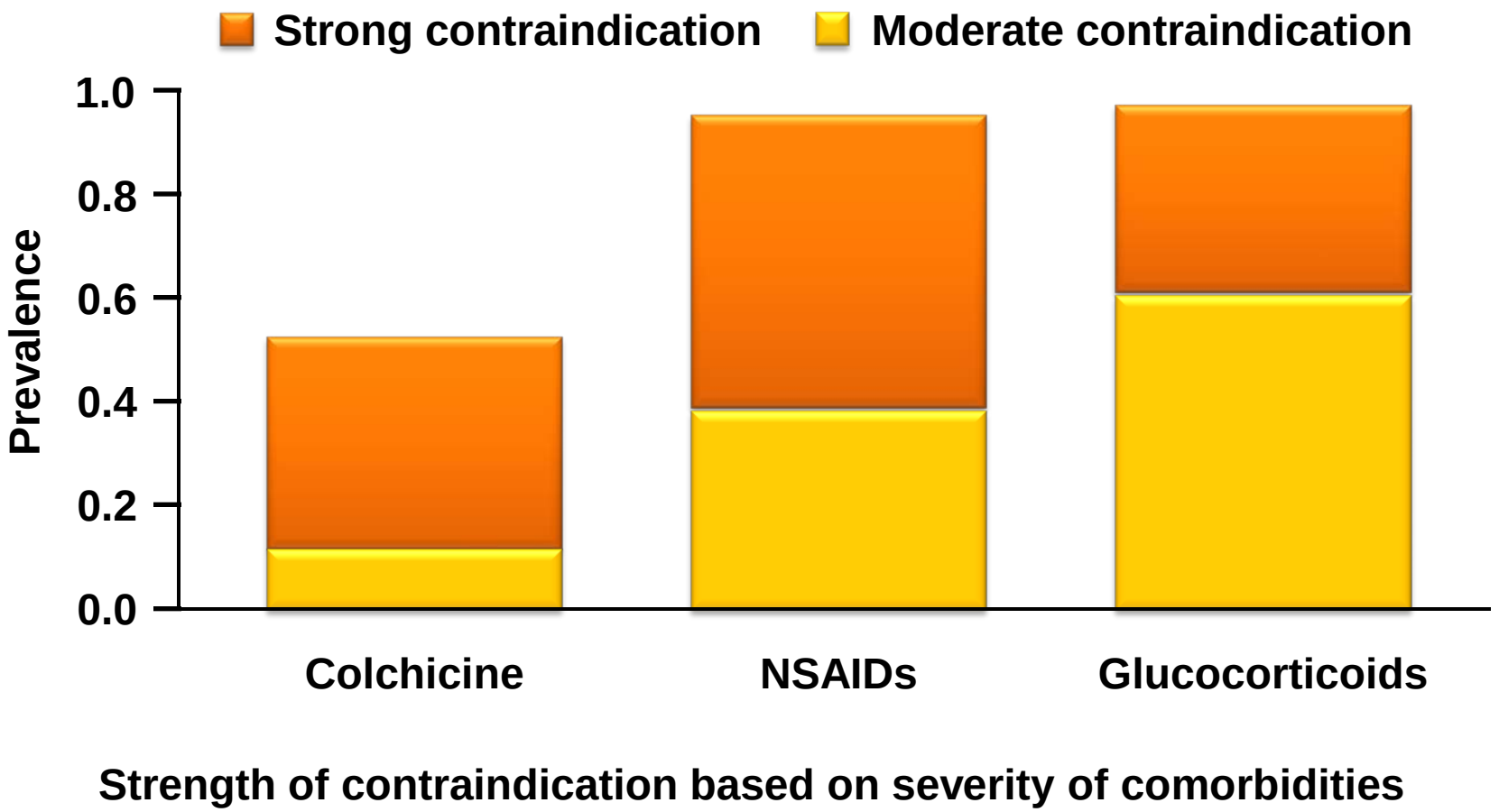
- Limited safety data for toxicity
- Drug-drug interactions
  - eg, statins, digoxin, ARVs, clarithromycin, ketoconazole, cyclosporin, calcium channel blockers
- Blood cytopenias
- Renal or hepatic impairment
- Neuromuscular toxicity
- Tolerability
  - GI: diarrhea, vomiting, nausea

NSAIDS

- Safety
  - Gastrointestinal
  - Cardiovascular
  - CHF
  - Renal impairment
  - Hypertension
- Tolerability
  - GI intolerance

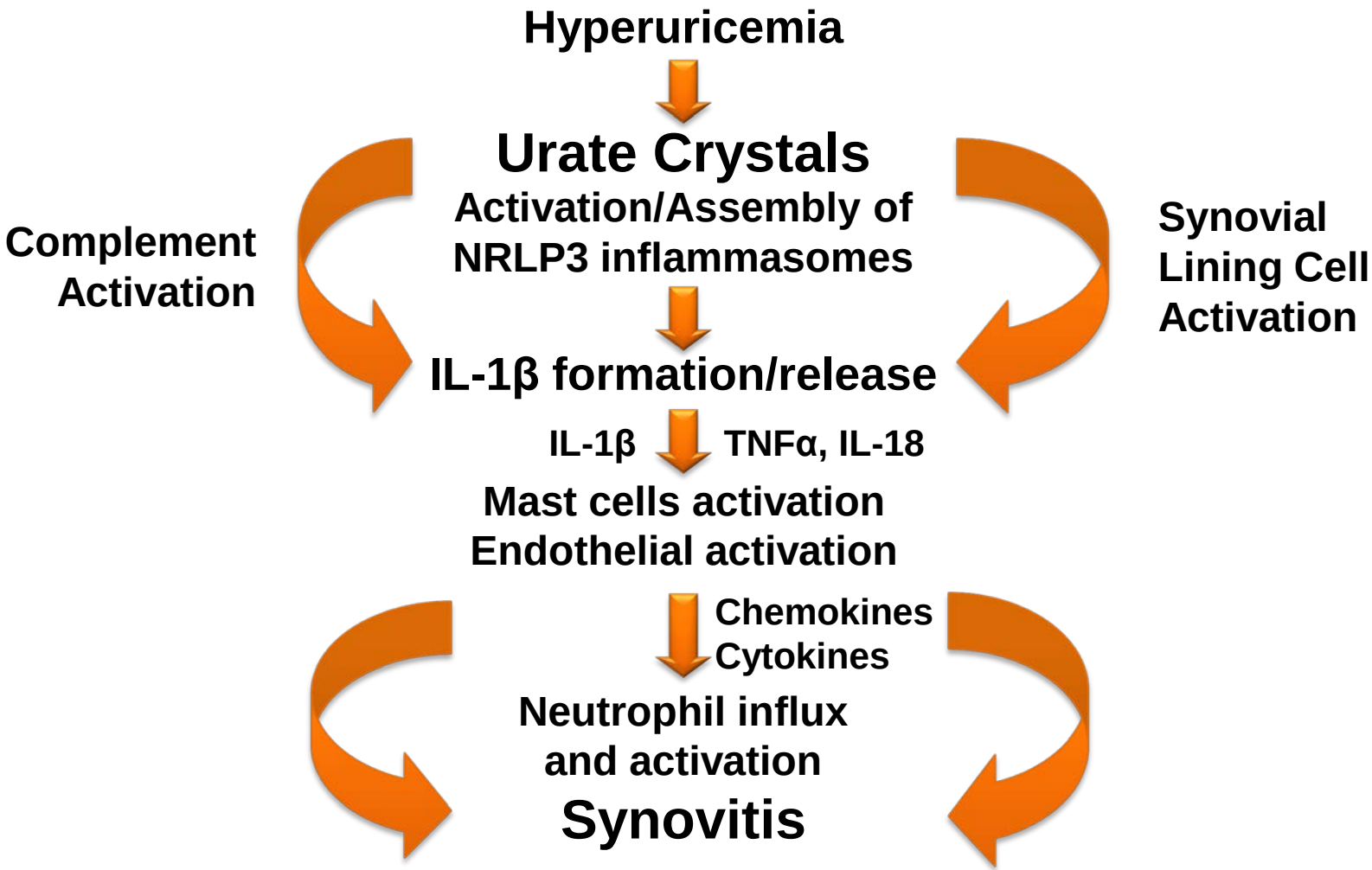
Based on Full Prescribing Information for naproxen, indomethacin, and colchicine.

Prevalence of Contraindications to Colchicine, NSAIDs, and Glucocorticoids Among 575 Patients with Gout



Adapted from Keenan et al. *Amer J Med.* 2011;124:155-163.

Pathophysiology of Acute Gouty Inflammation



Liu-Bryant et al. *Arthritis Rheum*. 2005; 52:2936; Martinon et al. *Nature*. 2006;440:237; Bieber et al. *Arthritis Rheum*. 2004;50:2400.

Additional Options Are Needed for Flare Prophylaxis During Urate-Lowering Therapy Initiation

- Flares during initiation of ULT discourage patient adherence to urate-lowering treatment
  - Significant disincentive due to morbidity and loss of productivity due to even a single flare
- Limitations of existing prophylaxis agents
  - Narrow therapeutic window with tolerability issues, limited safety profile, and numerous drug-drug interactions/contraindications
  - Safety concerns and contraindications especially notable in high-risk gout patient population with co-morbidities

Additional Options Are Needed for Flare Prophylaxis During Urate-Lowering Therapy Initiation

- A new drug for flare prevention (prophylaxis) should be:
  - a well-characterized agent with short duration of action (days) and minimal drug-drug interactions
  - efficacious
  - safe and well-tolerated in the high risk gout patient population, especially patients with tophi/polyarticular disease and those with co-morbidities
- If safe and effective, a drug targeting IL-1 could be a useful addition to gout flare prophylaxis

Clinical Development and Efficacy

Steven P. Weinstein, MD, PhD

Therapeutic Area Head, Immunology & Inflammation
Regeneron Pharmaceuticals, Inc.

Clinical Development for Rilonacept in Prevention of ULT-Induced Gout Flares

Over 1800 Patients / 1353 treated with rilonacept

Phase 2 trial

Study 0619

- Proof of efficacy (N=83)

Phase 3 trials

Study 0810

- Confirmatory efficacy (N=241)
  - US
  - Canada

Study 0816

- Confirmatory efficacy (N=248)
  - South Africa
  - India
  - Germany
  - Indonesia
  - Taiwan

Study 0815

- Large safety study (N=1315)
  - US
  - South Africa
  - India
  - Germany
  - Indonesia
  - Taiwan

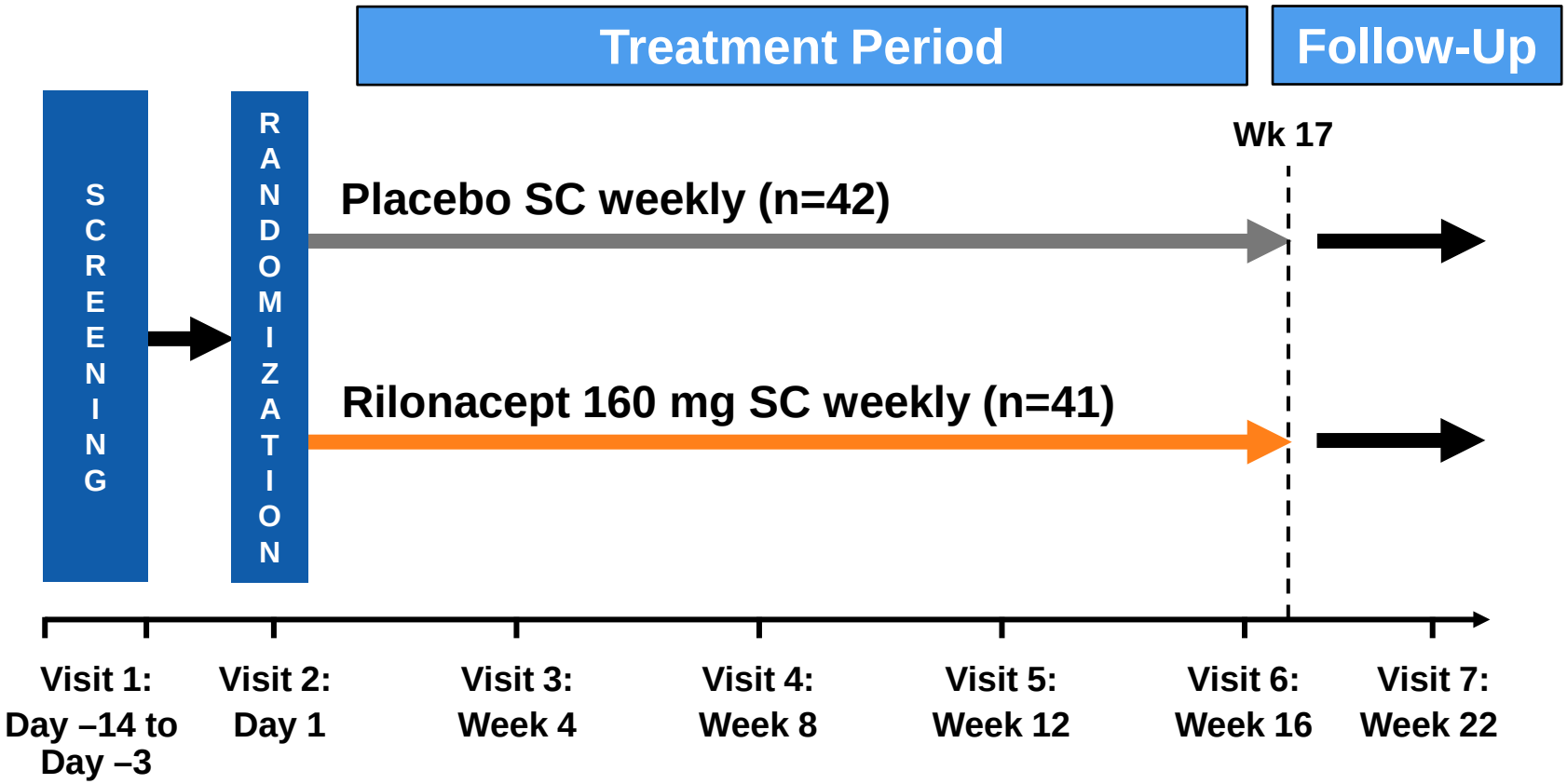
Rationale for Study Designs

- **16-Week Treatment Duration Includes Greatest Risk of Flares with ULT**
  - **Recommendations for duration of flare prophylaxis unclear**
  - **Greatest rate of gout flares in first 12 weeks, fewer in next 12 weeks (Borstad, et al)**

- **Placebo-Control Allows Rigorous Assessment and Broad Population**
  - **Colchicine and NSAIDs have not been rigorously evaluated in prophylaxis setting**
  - **Allows most rigorous assessment of absolute efficacy and safety**
  - **Allow study of broad population, including patients for whom colchicine and NSAIDs are inadvisable**

Phase 2 Study Design
Study 0619 (N= 83)

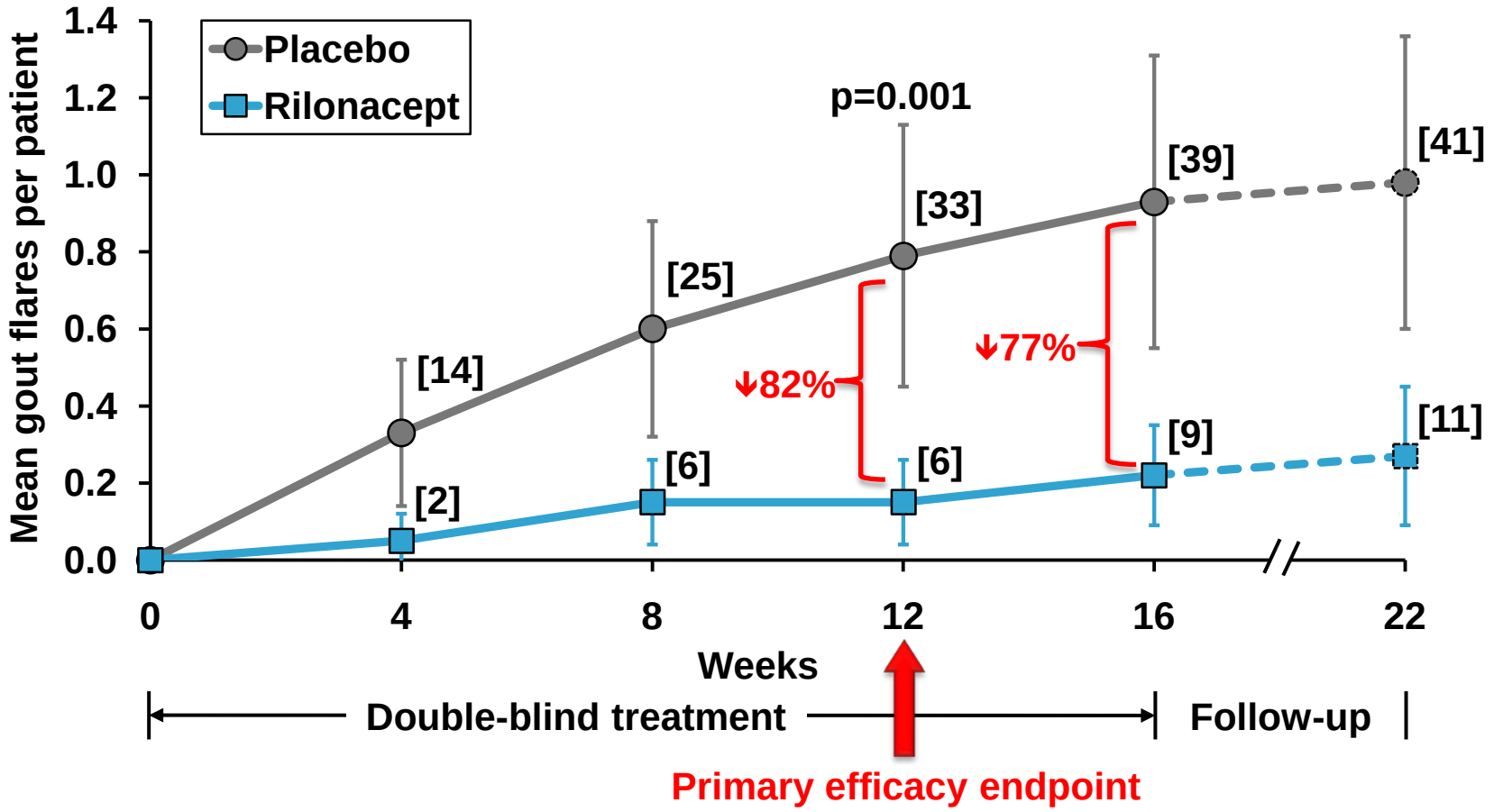
Used currently approved dose in CAPS: 160 mg weekly



- Loading dose of study drug on Day 1
- Initiate allopurinol 300 mg daily (all groups); titrate to achieve serum urate levels <6 mg/dL

Primary Endpoint: Cumulative Gout Flares Per Patient

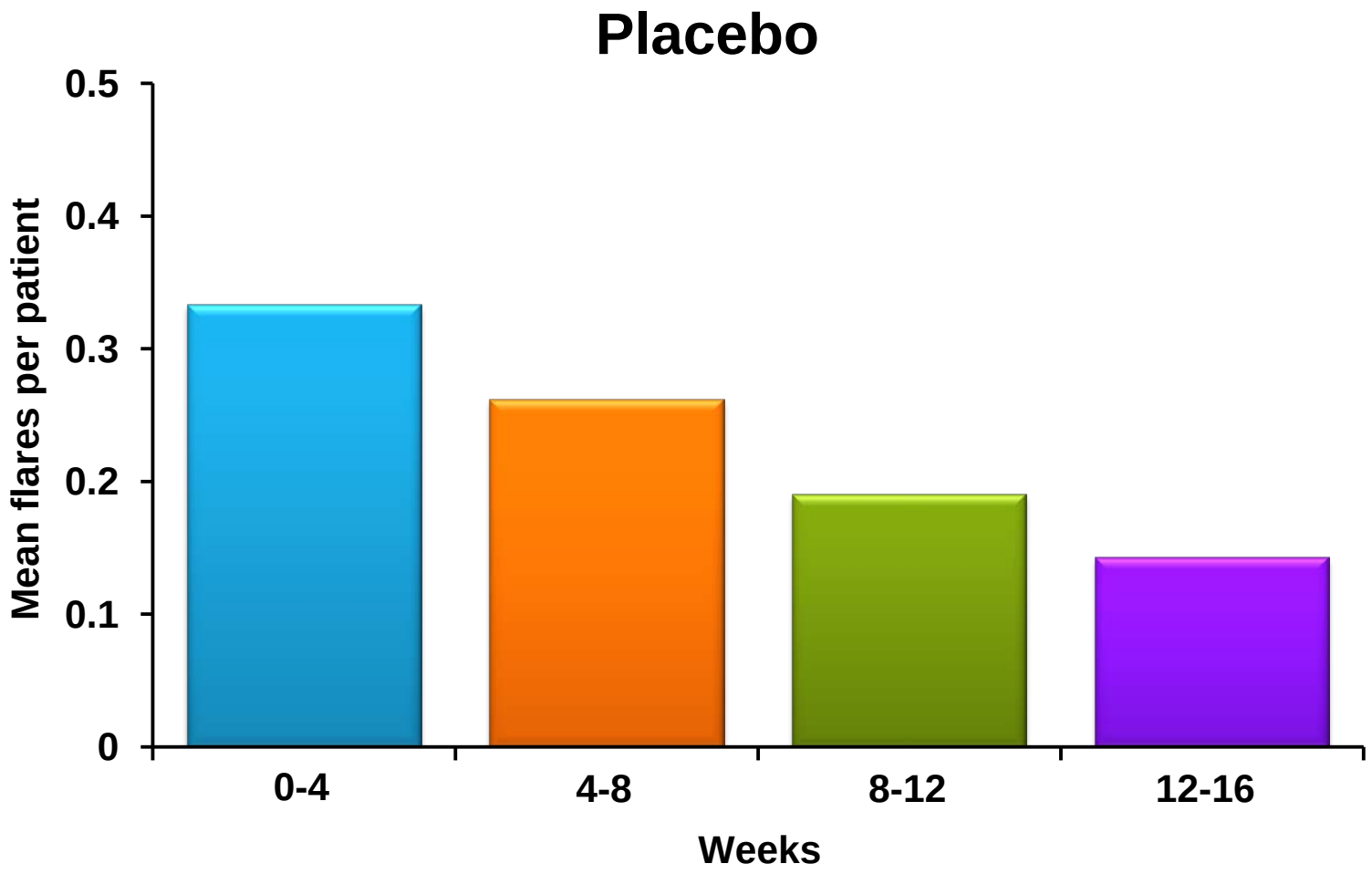
Phase 2 Study 0619



Numbers in brackets are cumulative number of gout flares

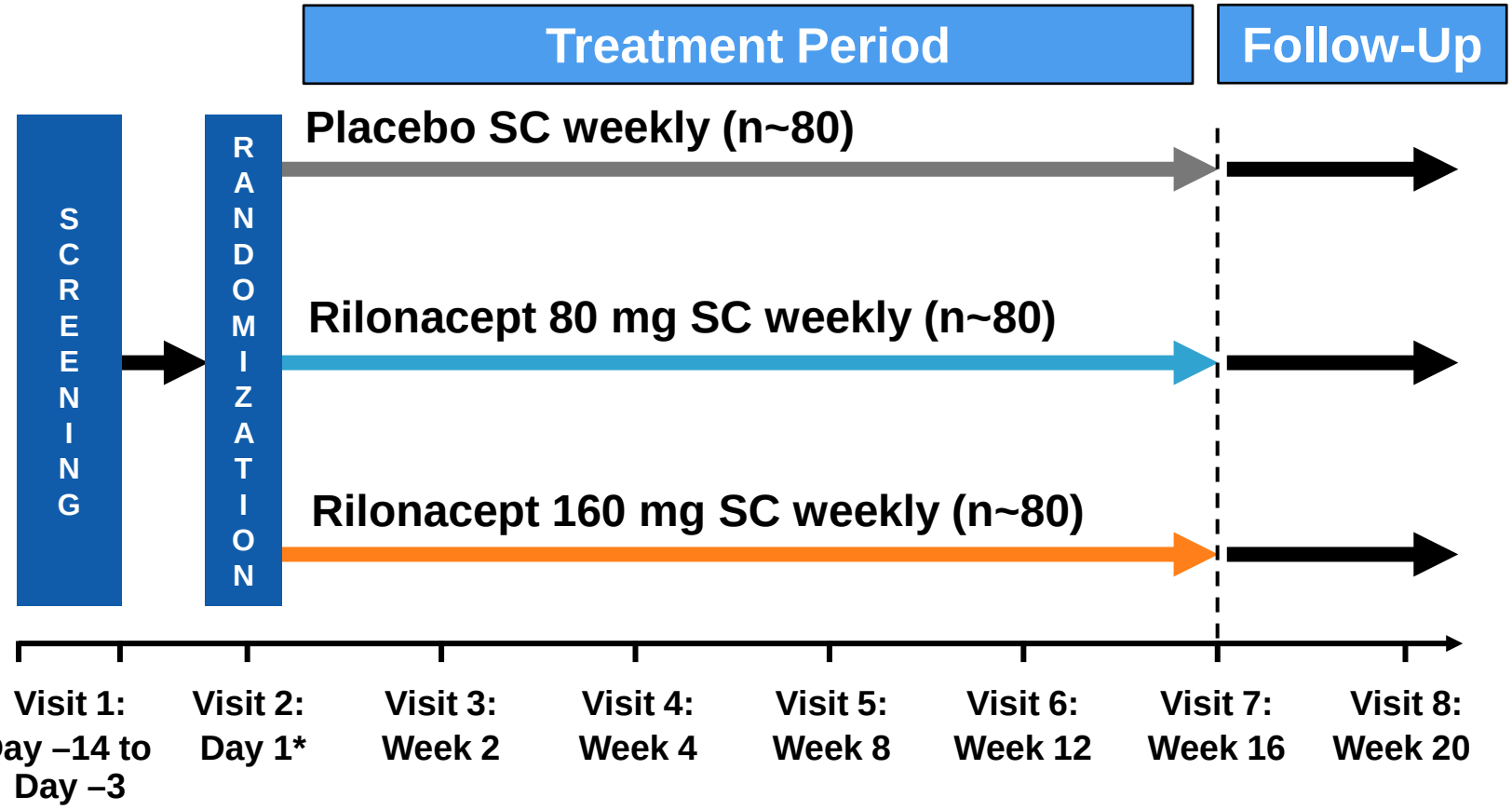
Gout Flares Decrease Over Time After Initiating ULT

Phase 2 Study 0619



Two Identical Confirmatory Phase 3 Efficacy Studies

0810 (N = 241) and 0816 (N = 248)



Allopurinol initiated Day 1 (all groups); titrated to achieve serum urate levels <6 mg/dL

Phase 3 Program Included Large Placebo-Controlled Safety Study 0815

N=1315 / Also Prospectively Evaluated Efficacy

Phase 3 Safety Study with Prospective Efficacy Endpoints

- **Global Study**
- **Total of 1315 patients continuing or initiating ULT**
- **3:1 randomization of 160 mg rilonacept to placebo**
- **16 week treatment duration, with 4-week follow-up, as in confirmatory Phase 3 efficacy studies**
- **Prospective efficacy endpoints:**
  - **Mean number of flares per patient**
  - **Proportion of patients with flares**

Definitions of Gout Flare

- All patient-reported flares were captured
- Gout flare definition for phase 2 and phase 3 safety study:
  - Patient-reported acute articular pain typical of a gout attack, and treatment with anti-inflammatory therapeutic
- Gout flare definition for phase 3 efficacy studies:
  - Phase 2 definition PLUS:
    - At least 2 of the following 3 additional signs/symptoms:
      - Joint swelling; redness; tenderness
    - At least 1 of the following:
      - Rapid onset of pain; decreased joint range of motion; joint warmth; or other symptoms similar to a prior gout flare
- Similar results regardless of definition used

Efficacy Endpoints
Phase 3 Confirmatory Efficacy Studies 0810 and 0816

Primary endpoint

- Mean number of gout flares

Secondary endpoints

- Proportion of patients with ≥1 gout flares
- Proportion of patients with ≥2 gout flares
- Mean number of gout flare days per subject
- Mean number of days with pain score ≥5 out of 10
- Mean number of gout flares using “Phase 2 Definition”

Key Eligibility Criteria

Phase 3 Confirmatory Efficacy Studies 0810 and 0816

Inclusion

- Patients 18-80 years
- Confirmed gout by ≥6 of 13 criteria of the American Rheumatism Association (ARA)
- Serum uric acid ≥7.5 mg/dL
- A self-reported history of ≥2 gout flares in the prior year

Exclusion

- Acute gout flare within the prior two weeks
- Active infection or recent treatment with anti-infective agents
- Absolute contraindication to both NSAIDs AND glucocorticoids
- Patients inappropriate for treatment with allopurinol

Demography and Baseline Characteristics

Phase 3 Confirmatory Efficacy Studies 0810 and 0816

	Study 0810			Study 0816		
	Placebo n=79	Rilonacept 80 mg n=80	Rilonacept 160 mg n=81	Placebo n=82	Rilonacept 80 mg n=82	Rilonacept 160 mg n=84
Gender, %						
Male	96.2	88.8	93.8	93.9	93.9	91.7
Female	3.8	11.3	6.2	6.1	6.1	8.3
Age, yr						
Mean (SD)	52.2 (13.6)	52.9 (12.5)	51.9 (11.6)	51.7 (12.9)	52.6 (11.5)	49.0 (11.8)
<65, %	78.5	81.3	84.0	85.4	81.7	90.5
≥65, %	21.5	18.8	16.0	14.6	18.3	9.5
BMI, kg/m^2						
Mean (SD)	33.1 (7.6)	33.3 (6.3)	33.3 (6.7)	31.78 (6.4)	30.0 (5.8)	30.5 (5.5)
<30, %	41.8	33.8	37.0	46.3	50.0	51.2
≥30, %	58.2	66.3	63.0	53.7	50.0	48.8
Race, %						
White	81.0	75.0	85.2	52.4	54.9	52.4
Black or African American	13.9	18.8	12.3	12.2	17.1	11.9
Asian	5.1	6.3	1.2	35.4	28.0	35.7

Baseline Disease Characteristics and Gout History

Phase 3 Confirmatory Efficacy Studies 0810 and 0816

	Study 0810			Study 0816		
	Placebo n=79	Rilonacept 80 mg n=80	Rilonacept 160 mg n=81	Placebo n=82	Rilonacept 80 mg n=82	Rilonacept 160 mg n=84
Duration of disease, yr						
Mean (SD)	11.2 (9.4)	9.1 (8.3)	10.0 (8.3)	9.6 (8.8)	12.6 (10.3)	8.7 (7.0)
Median	10.0	6.0	8.0	6.0	9.5	7.5
Uric acid level, mg/dL						
Mean (SD)	9.4 (1.4)	9.0 (1.2)	9.1 (1.2)	9.4 (1.4)	9.4 (1.5)	9.5 (1.5)
Median	9.5	9.1	9.0	9.2	9.0	9.4
Gout flares in prior year, n						
Mean (SD)	4.6 (3.6)	4.6 (2.9)	4.5 (3.6)	7.1 (6.9)	6.8 (5.4)	7.0 (5.7)
Median	4.0	4.0	3.0	5.0	5.0	5.0
Visible tophi present, %	10.1	12.5	9.9	22.0	25.6	25.0
Polyarticular disease present, %	79.7	68.8	65.4	82.9	76.8	79.8

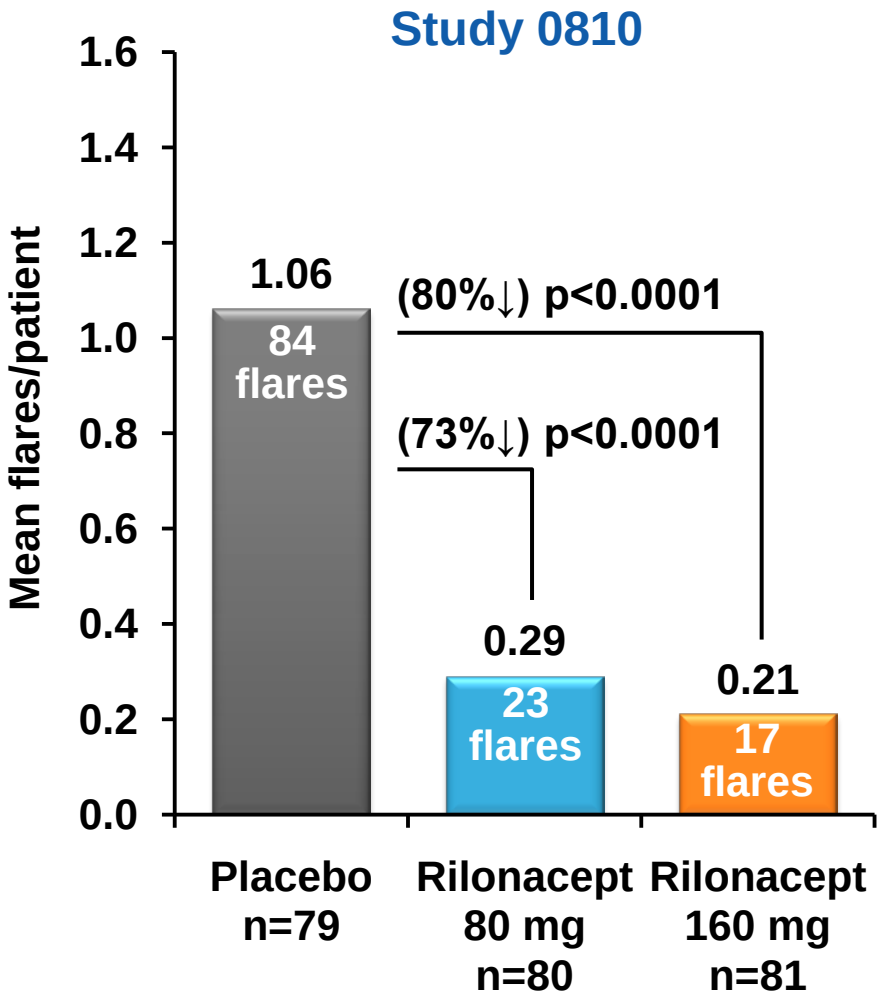
Patient Disposition

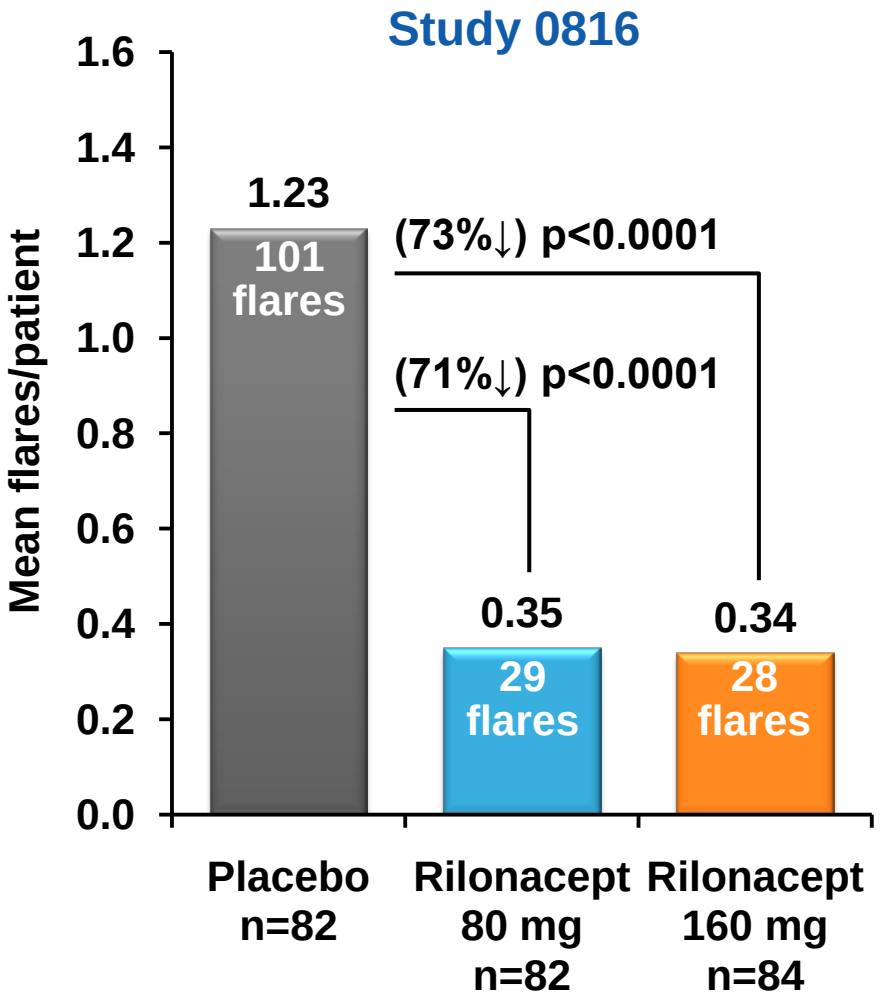
Phase 3 Confirmatory Efficacy Studies 0810 and 0816

	Patients, %					
	Study 0810			Study 0816		
	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	Placebo	Rilonacept 80 mg	Rilonacept 160 mg
Randomized, n	80	80	81	82	82	84
Full Analysis Set (FAS)	98.8	100	100	100	100	100
Patients dosed	98.8	100	100	100	100	100
Withdrawals before week 16	27.5	20.0	13.6	12.2	12.2	7.1
Reason for early withdrawal before week 16						
Non-compliance with protocol	0	3.8	0	3.7	2.4	2.4
Adverse event	5.0	5.0	3.7	0	3.7	0
Request by patient	10.0	5.0	2.5	4.9	2.4	1.2
Decision by the sponsor	1.3	0	2.5	1.2	0	1.2
Lost to follow up	8.8	3.8	3.7	0	0	0
Other	2.5	2.5	1.2	2.4	3.7	2.4

Primary Endpoint: Number of Gout Flares per Patient

Phase 3 Confirmatory Efficacy Studies 0810 and 0816

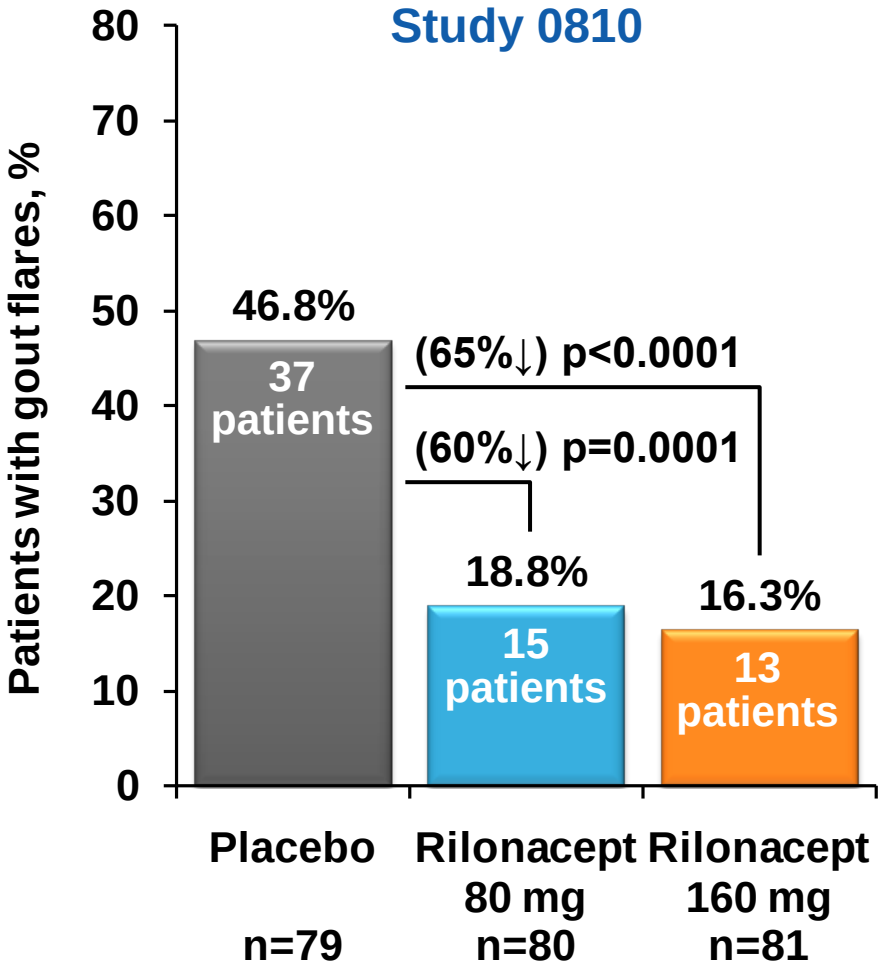


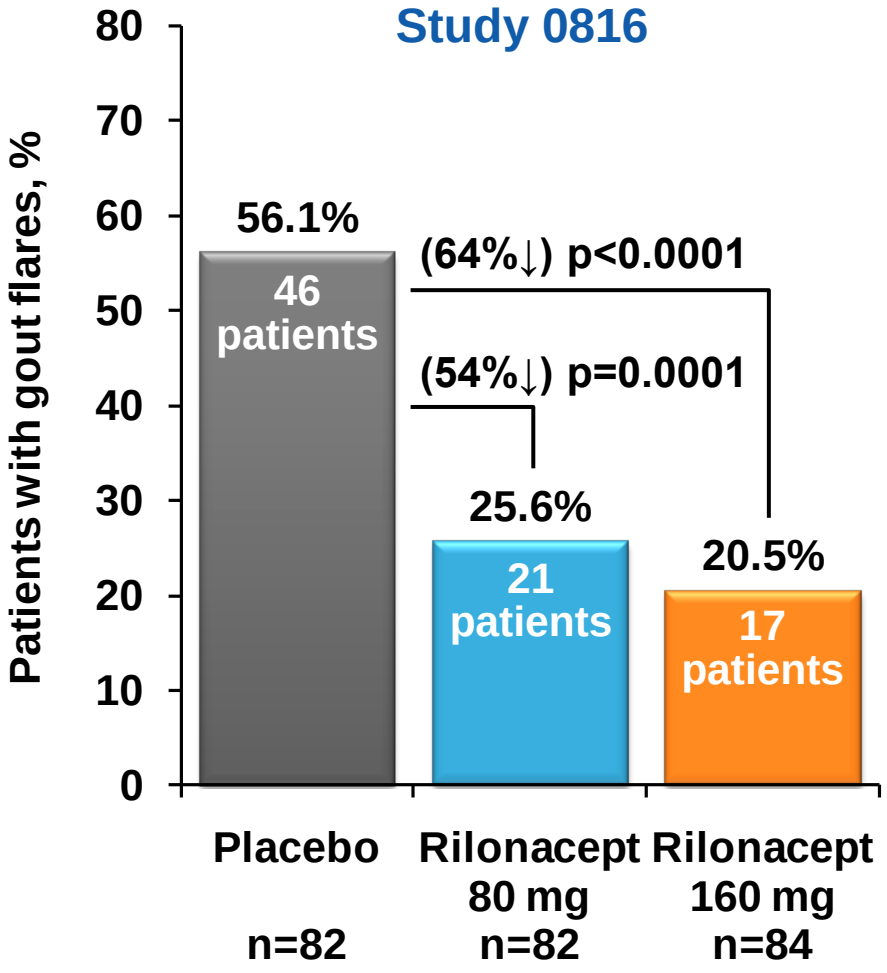


Wilcoxon Rank Sum test.

Key Secondary Endpoint: Proportion of Patients with ≥1 Gout Flare

Phase 3 Confirmatory Efficacy Studies 0810 and 0816

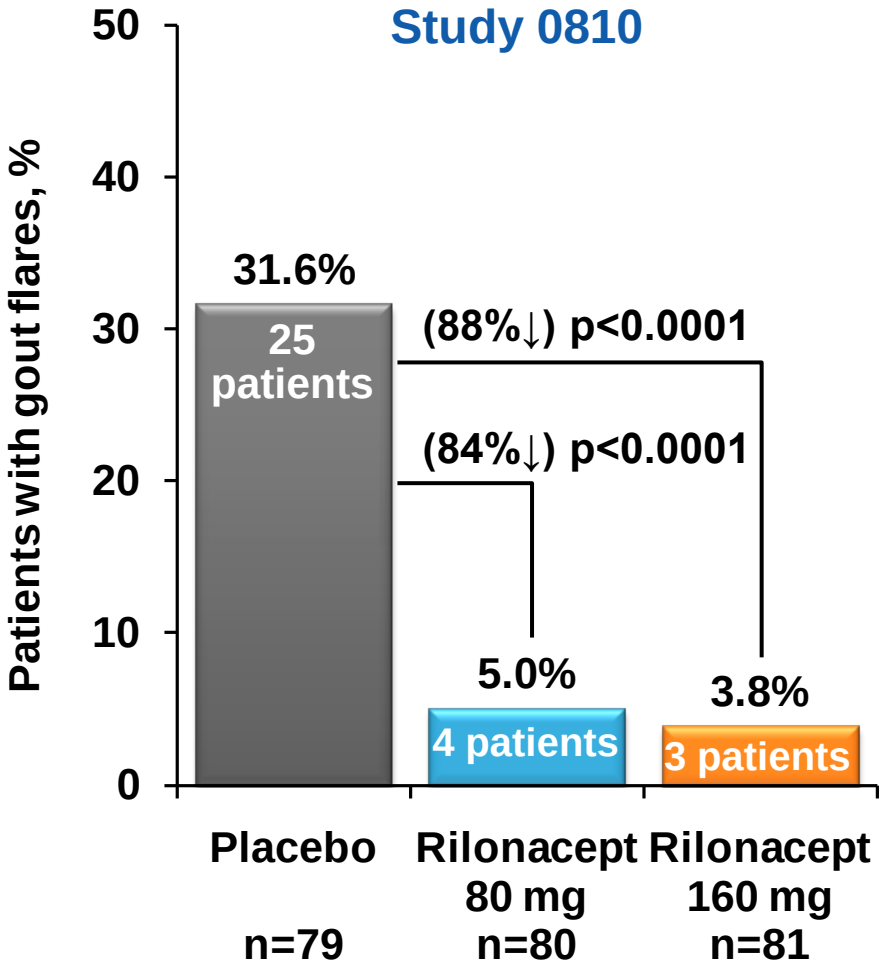


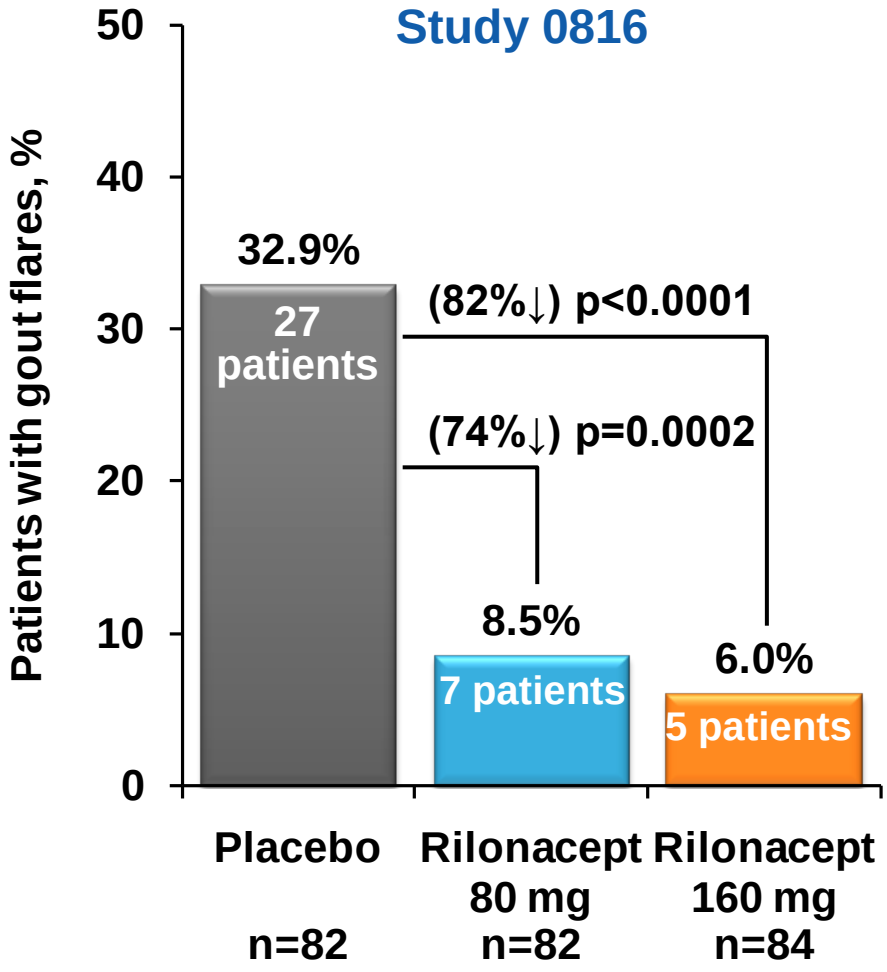


Fisher's Exact test.

Key Secondary Endpoint: Proportion of Patients with ≥2 Gout Flares

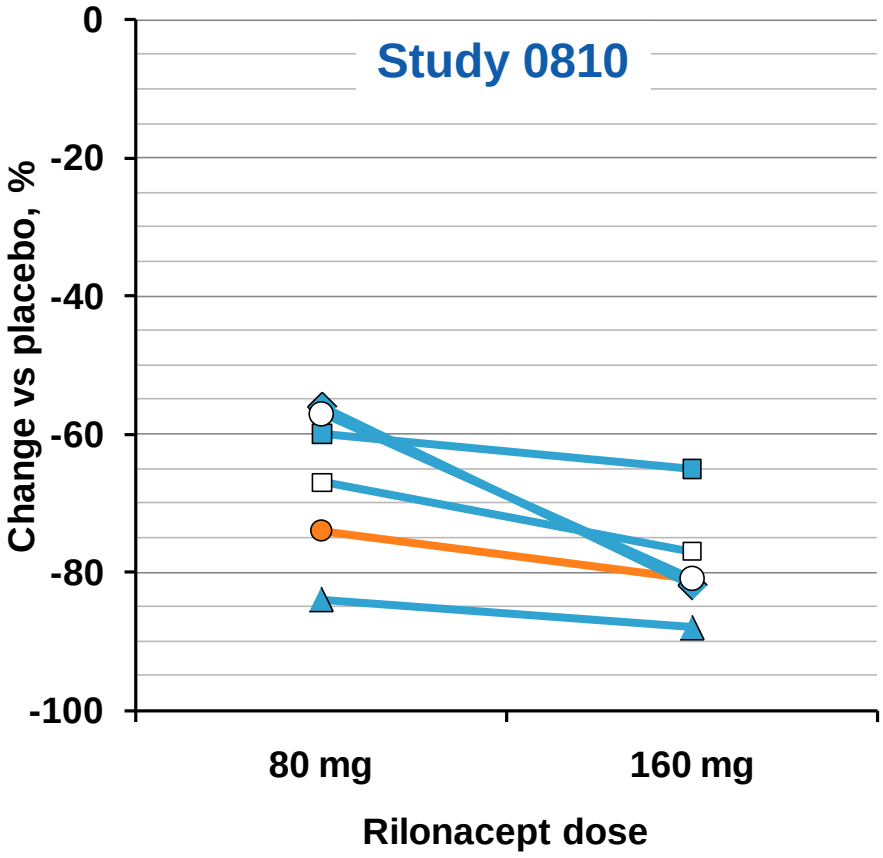
Phase 3 Confirmatory Efficacy Studies 0810 and 0816

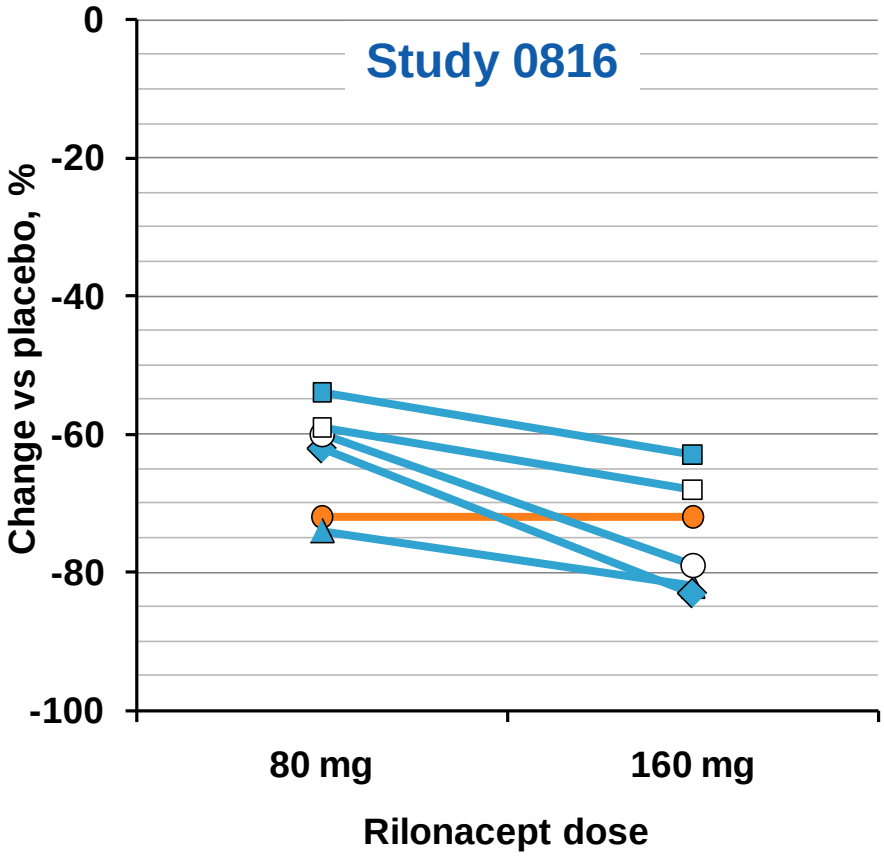




Fisher's Exact test.

Both Rilonacept Doses Effective
Doses <80mg Would Likely Be Less Effective
Phase 3 Confirmatory Efficacy Studies 0810 and 0816



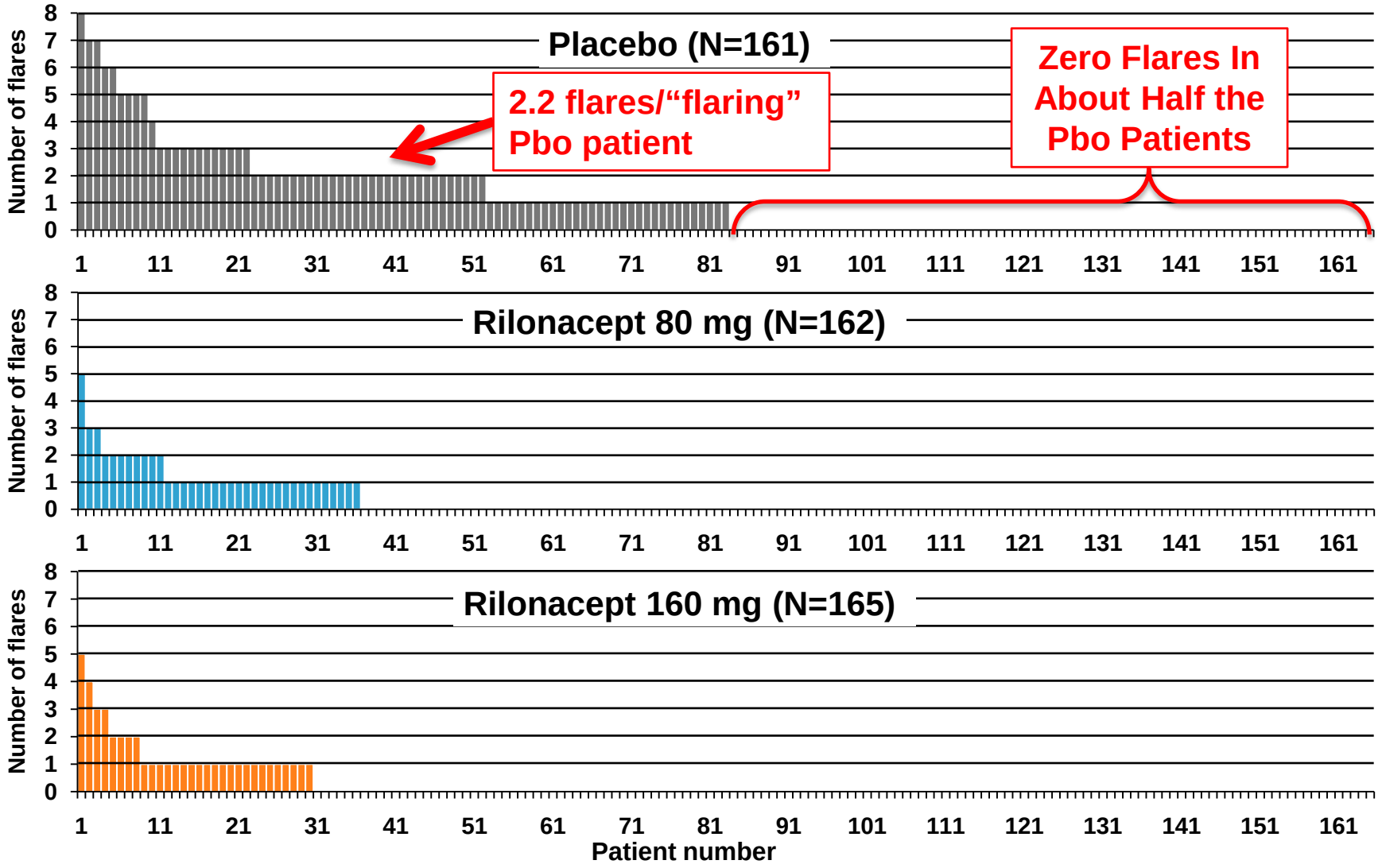


1°: Flares/patient

2°:%≥ 1 flare | 2°: %≥ 2 GF | 2°: Flares/patient | Days w/ flare | Days w/ Flare pain ≥ 5

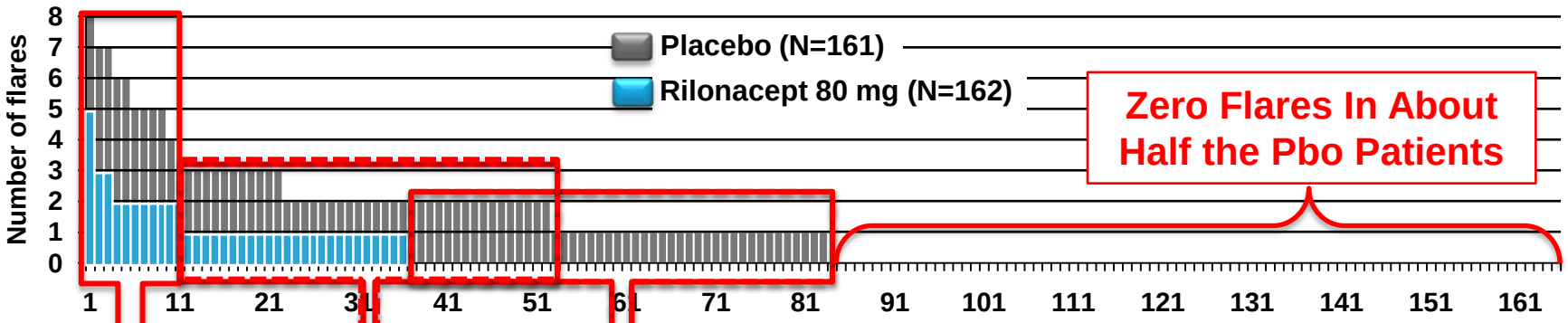
Number of Gout Flares by Patient

Phase 3 Confirmatory Efficacy Studies 0810 and 0816



NNT Calculations Must Be Combined To Reflect Total Population Benefit (NNT ~2)

Phase 3 Confirmatory Efficacy Studies 0810 and 0816



Uncaptured Flare Reduction Benefit

~25% Patients Go to <2 Flare (NNT ~ 4)*

*FDA BB: Table 3 (80mg) (Columns 6, 8)

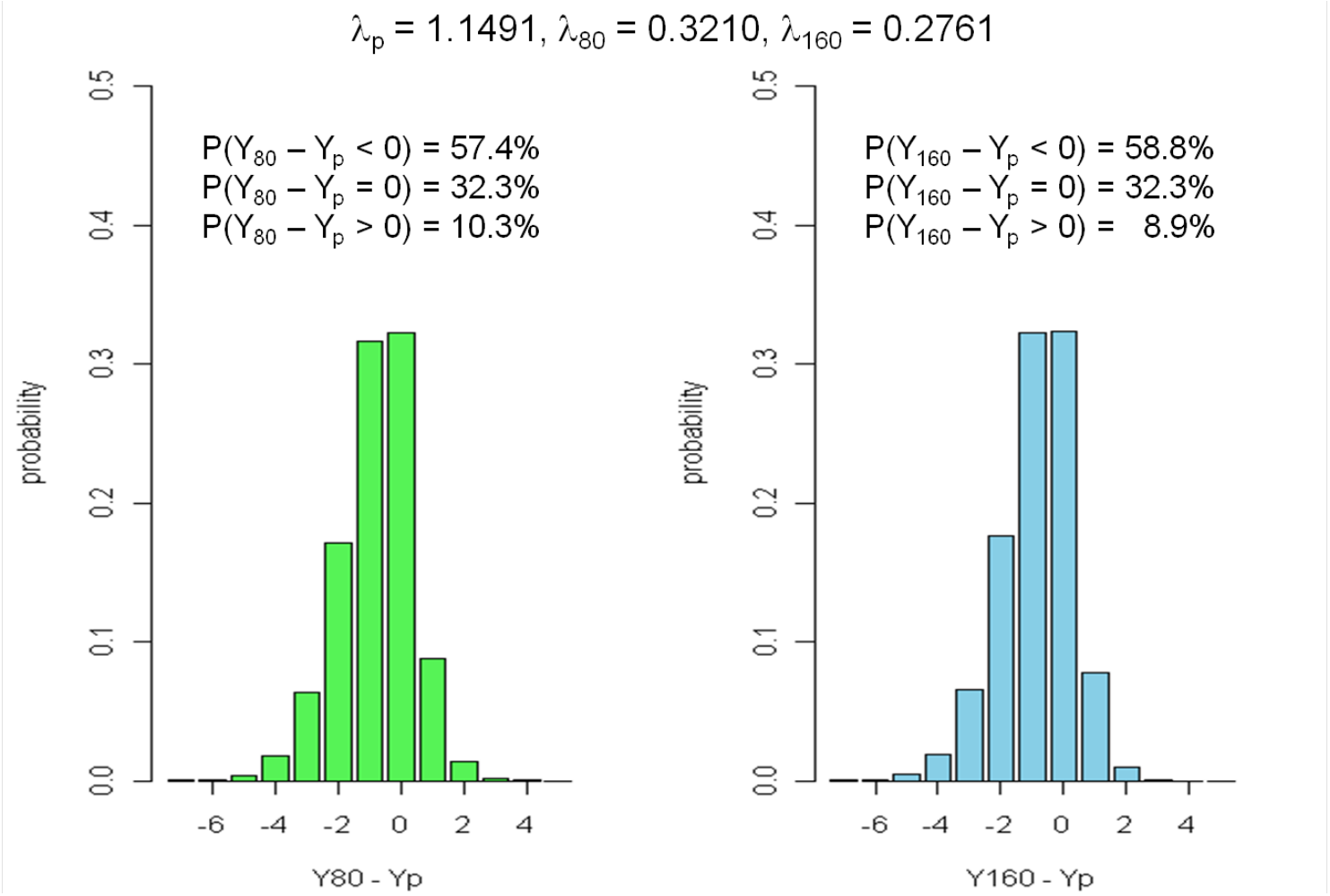
~30% Patients Go to <1 Flares (NNT ~ 4)*

*FDA BB: Table 3 (80mg) (Columns 5, 7)

Individual NNT Calculations Reflect Partially Overlapping Measures That Must Be Combined To Reflect Total Population Benefit:

Combining across these populations indicates about half the population benefits, resulting in NNT of about 2

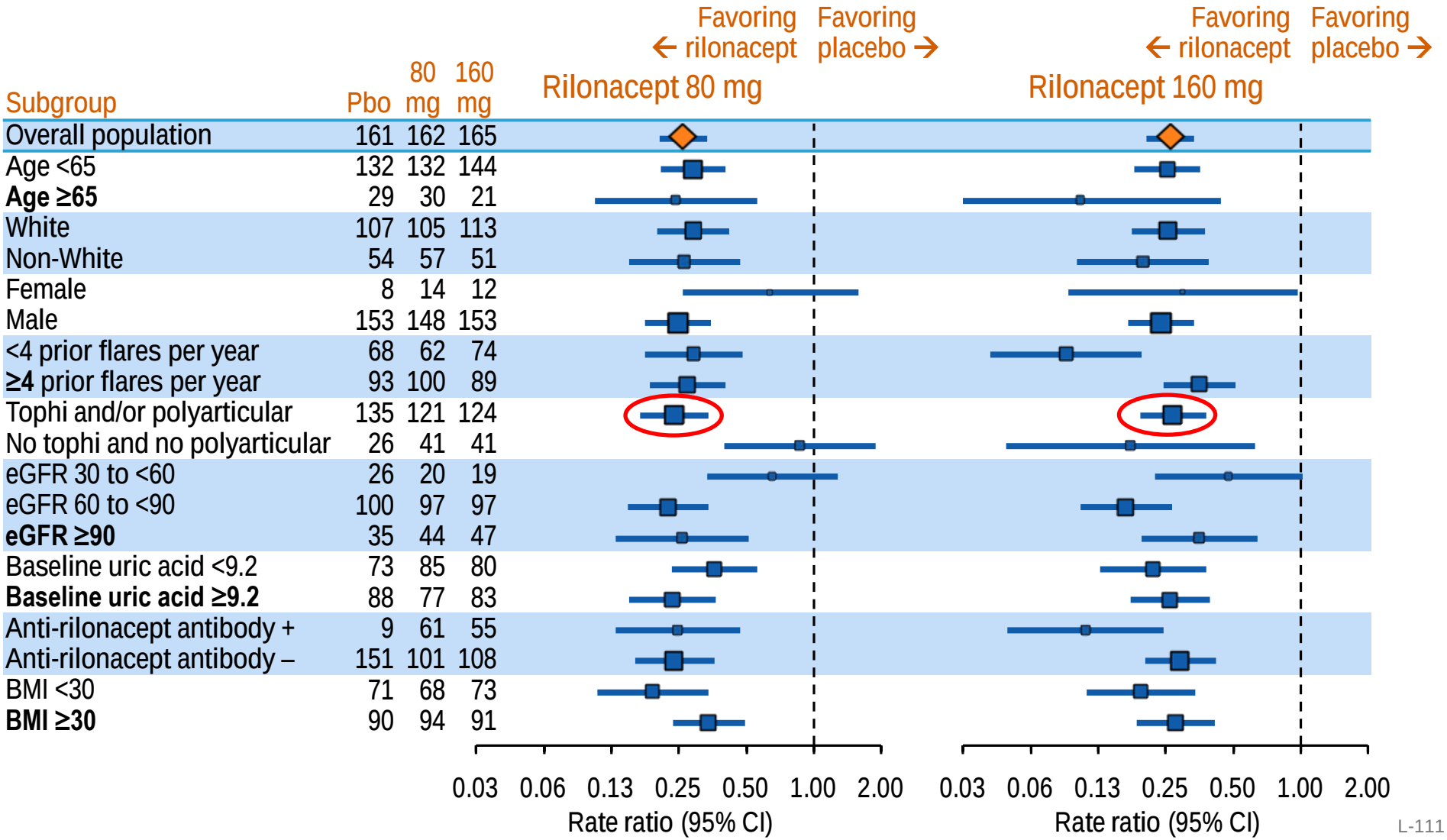
Skellam Distribution Estimates Total Population Benefit of About 50 Percent



Conditional expectation of benefit in the (Y_{80}-Y_p<0) patients that would flare on Placebo is 1.65 fewer flares

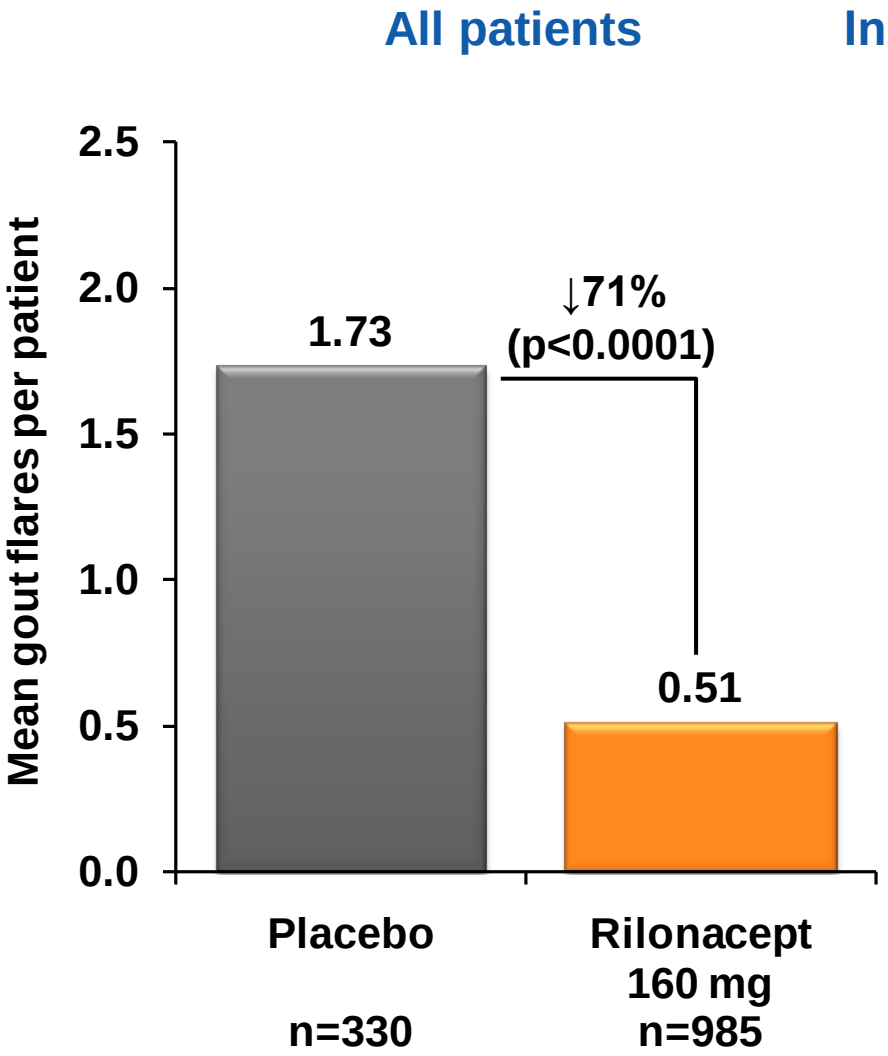
Subgroup Analyses of Primary Endpoint by Dose (Pooled Data)

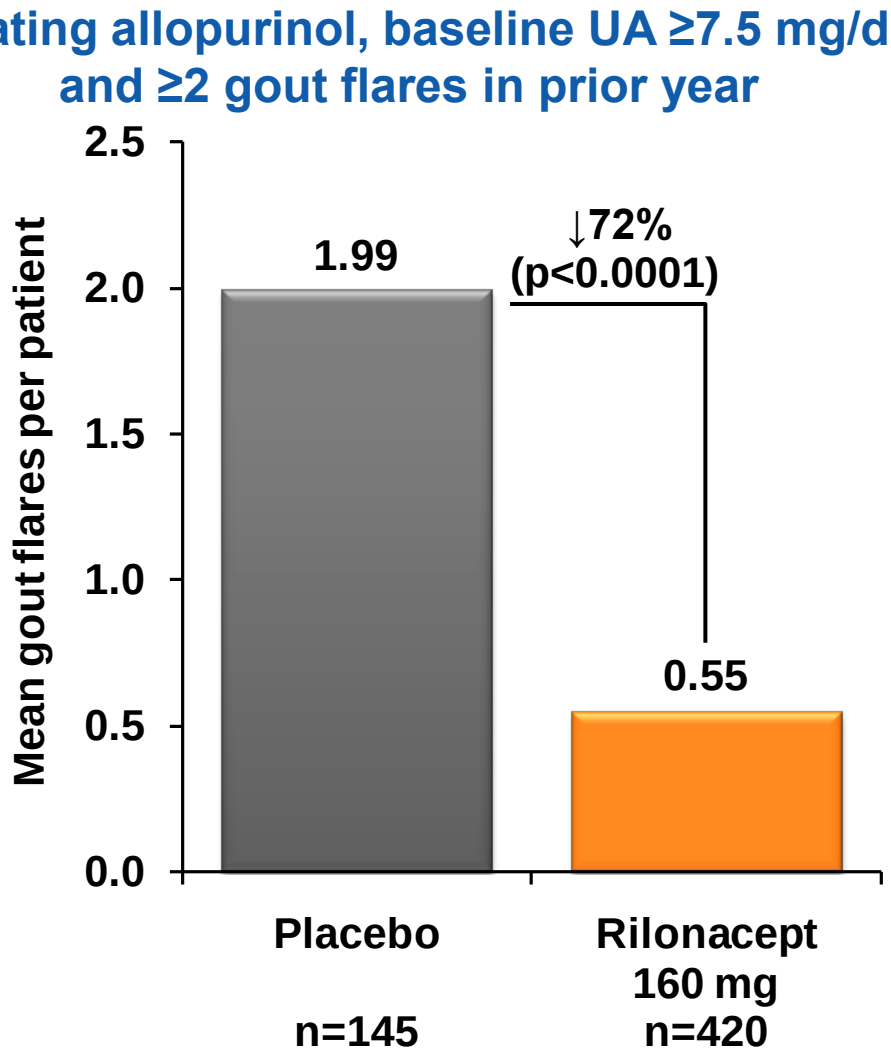
Phase 3 Confirmatory Efficacy Studies 0810 and 0816



Mean Gout Flares per Patient— All Patients vs Patients Initiating Allopurinol

Phase 3 "Safety" Study 0815



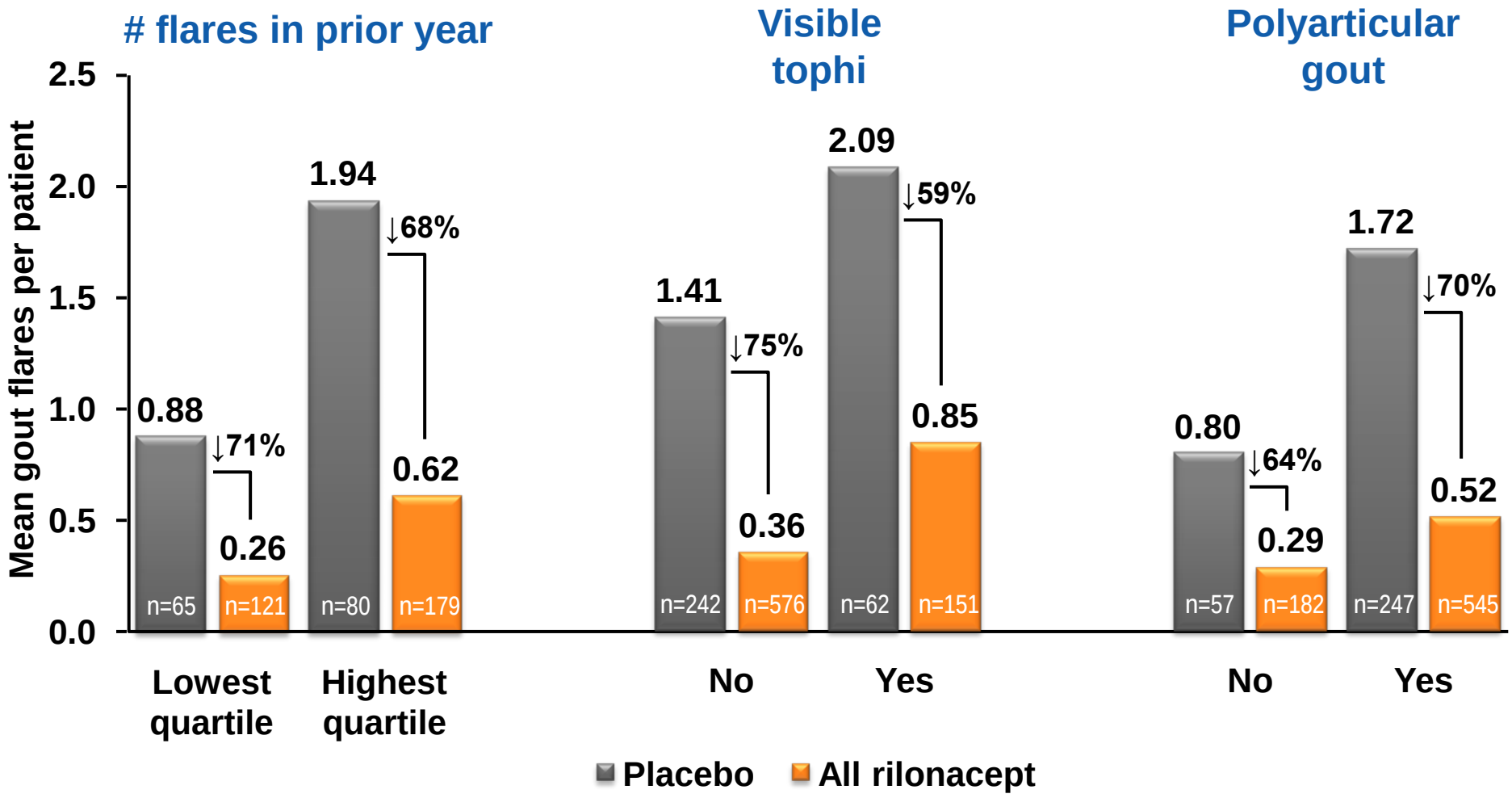


Note: Analyses shown use phase 2 flare definition.

L-118 0815 CSR Table 15.5.1

Mean Gout Flares Per Patient: Day 1 to Wk 16 (Subgroup Analyses)

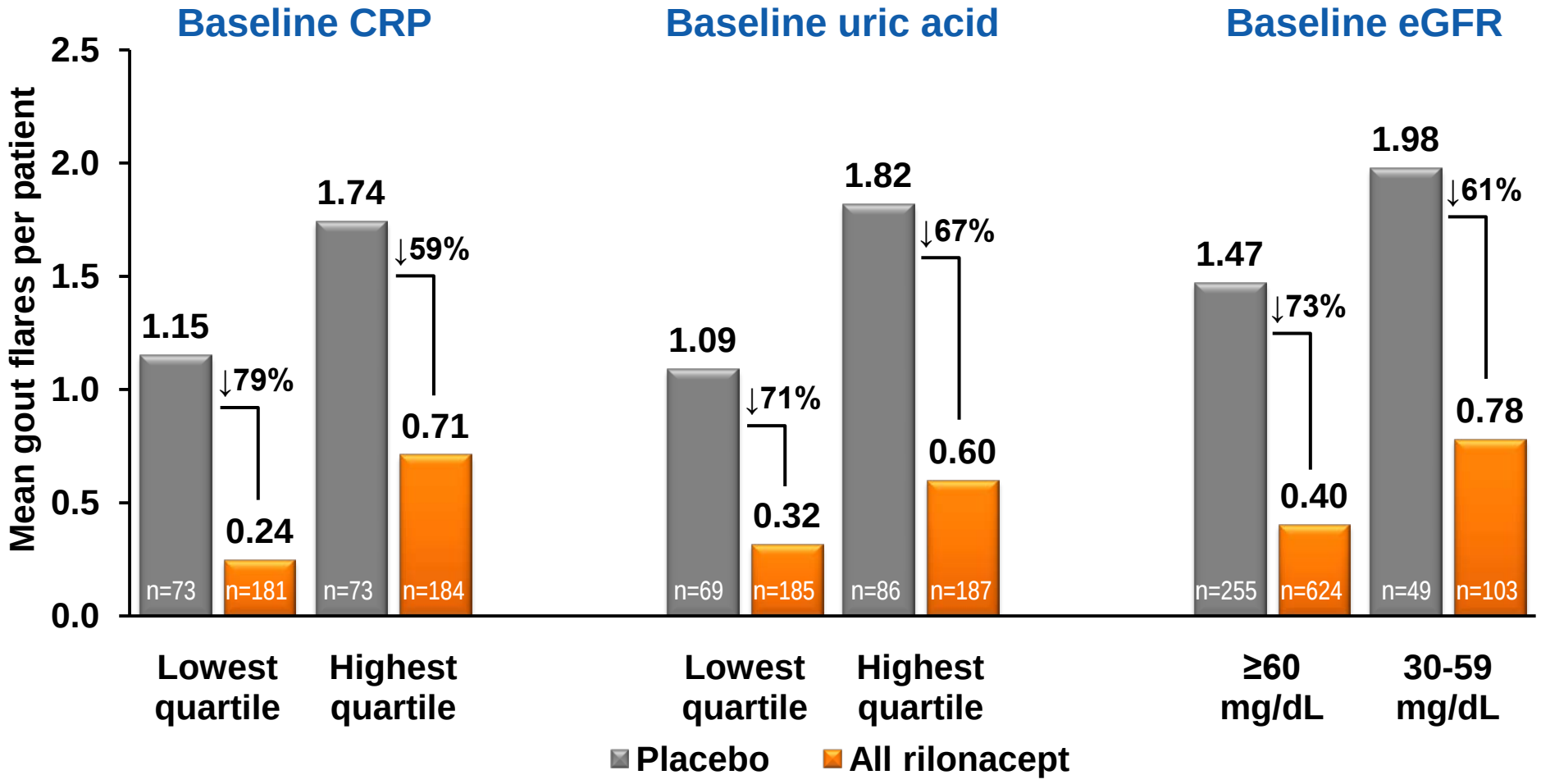
All Phase 3 Studies (0810, 0816, and 0815 combined)



Note: Uses flare definition 2. Includes only patients initiating allopurinol at baseline, with at least 2 flares in the prior year, and uric acid ≥7.5 mg/dL at baseline.

Mean Gout Flares Per Patient: Day 1 to Wk 16 (Subgroup Analyses)

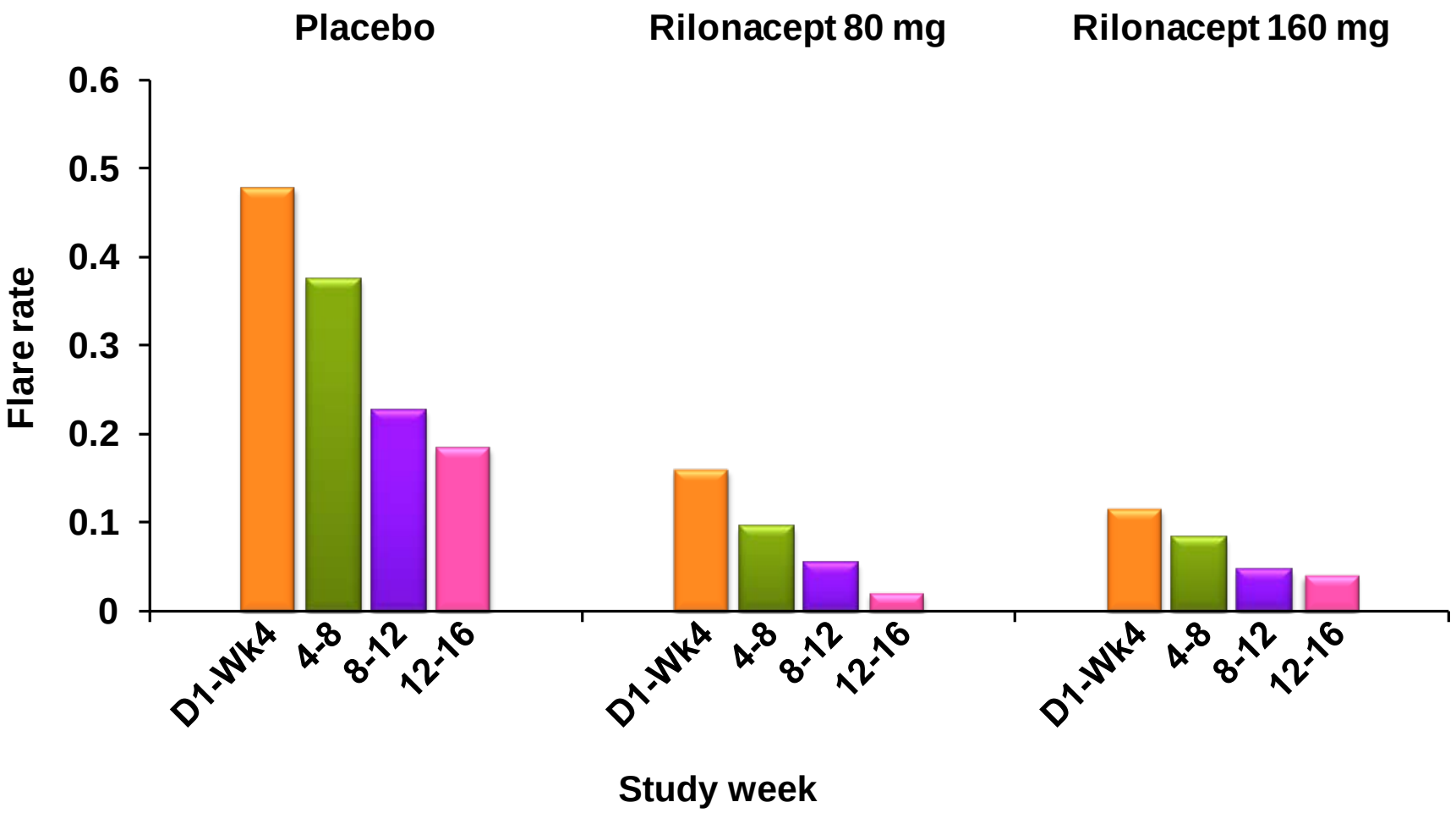
All Phase 3 Studies (0810, 0816, and 0815 combined)



Note: Use of flare definition 2. Includes only patients initiating allopurinol at baseline, with at least 2 flares in the prior year, and uric acid ≥7.5 at baseline.

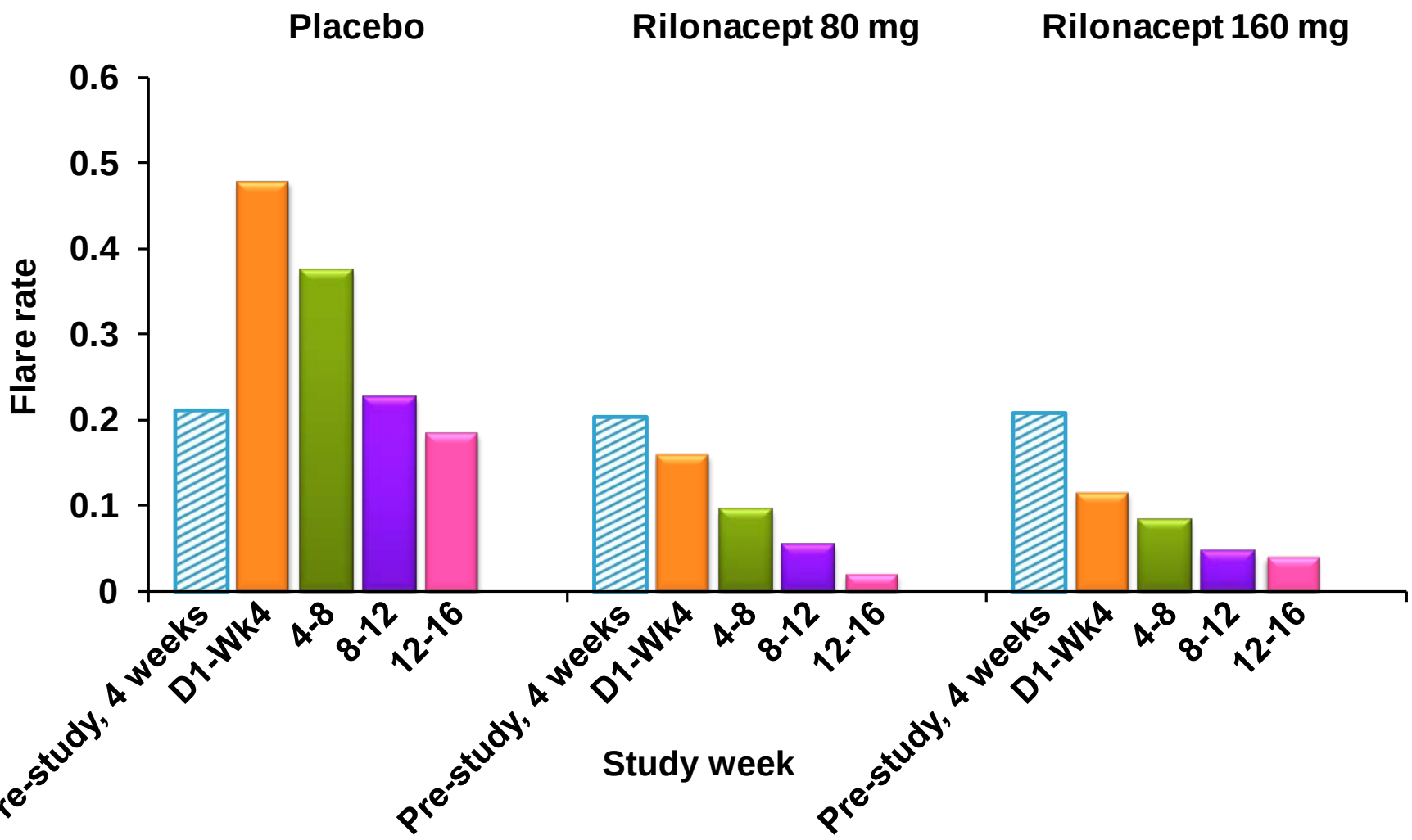
Gout Flares Decrease Over Time After Initiating ULT—Mean Flares per Patient by 4-week Period and by Treatment Group

Studies 0810 and 0816 Combined—Week 16



Gout Flares Decrease Over Time After Initiating ULT—Mean Flares per Patient by 4-week Period and by Treatment Group

Studies 0810 and 0816 Combined—Week 16



Gout Flares Decrease Over Time After Initiating ULT—Mean Flares per Patient by 4-week Period and by Treatment Group

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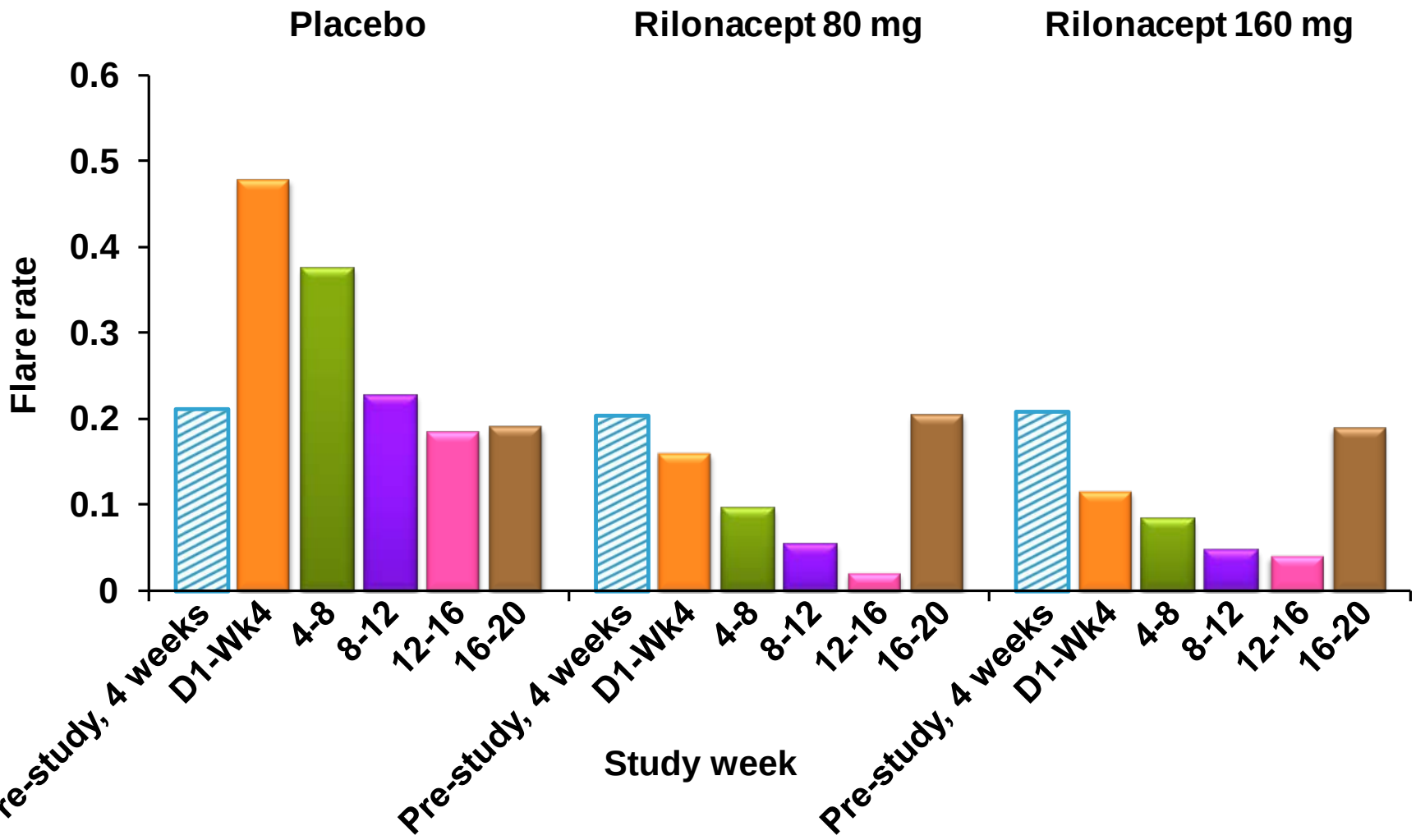


Rilonacept Reduces the Risk for Gout Flares in Patients Initiating Uric Acid-Lowering Therapy

- **Rilonacept significantly reduced gout flare rate compared to placebo in patients initiating ULT**
  - **Demonstrated efficacy at 16 weeks in primary and all secondary endpoints**
- **Rilonacept was similarly effective across subgroups**
  - **Including patients with greater burden of disease for whom clinicians might choose to prescribe this treatment**
- **Rilonacept 80 and 160 mg were consistently superior to placebo**
  - **Consistently (slightly) greater efficacy with 160 mg dose**
- **A 16-week course of treatment with rilonacept appears sufficient to eliminate the excess flares associated with initiating uric-acid lowering therapy**

Safety

Ned Braunstein, MD

Head of Regulatory Affairs

Clinical Development and Regulatory Affairs
Regeneron Pharmaceuticals, Inc.

Safety Summary

- Safety data support a positive benefit-risk for gout patients treated up to 16 weeks
- No increase in adverse events related to mechanism of action or patient comorbidities
  - Small numeric imbalance in neoplasms does not appear to be treatment related
- Safety data mostly 160 mg, twice the proposed 80 mg dose for gout
- Plans include appropriate labeling, physician education, and a registry
- Ongoing 1-year safety study

Safety Analysis Population
Overall Safety Population

	Numbers of patients				
Study	Placebo	Rilonacept 80 mg	Rilonacept 160 mg	Rilonacept any dose	All combined
Totals	**533**	**162**	**1191**	**1353**	**1886**
0810	79	80	81	161	240
0816	82	82	84	166	248
0815	330	—	985	985	1315
0619	42	—	41	41	83

Safety Database Requirements: End-of-Phase 2 Meeting

- At least 1000 patients studied for the duration we propose rilonacept should be used in clinical practice
- Communicated to FDA as IND amendment in December 2008

Demographics
Overall Safety Population

	Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
Age, yr				
Mean (SD)	52.1 (11.5)	52.7 (12.0)	52.4 (11.5)	52.4 (11.6)
Gender, n (%)				
Male	490 (91.9)	148 (91.4)	1050 (88.2)	1198 (88.5)
Female	43 (8.1)	14 (8.6)	141 (11.8)	155 (11.5)
BMI, kg/m^2				
Mean (SD)	31.9 (6.3)	31.6 (6.2)	32.2 (6.8)	32.1 (6.8)

Past Medical History
Overall Safety Population

	Patients, (%)			
	Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	Rilonacept any dose N=1353
Diabetes mellitus	12.2%	12.3%	13.2%	13.1%
Hyperlipidemia	13.7%	16.7%	12.2%	12.7%
Dyslipidemia	4.5%	7.4%	3.4%	3.8%
BMI ≥30, kg/m^2	58.0%	58.0%	56.7%	56.8%
Vascular disorders	55.2%	49.4%	53.6%	53.1%
Renal and urinary disorders	15.2%	16.0%	13.9%	14.2%
Cardiac disorders	11.4%	17.3%	11.3%	12.0%

Summary of Treatment-Emergent Adverse Events

Overall Safety Population

	Patients, n (%)			
	Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 TEAE	318 (59.7)	105 (64.8)	786 (66.0)	891 (65.9)
Severe TEAEs	24 (4.5)	6 (3.7)	64 (5.4)	70 (5.2)
Serious TEAEs	22 (4.1)	8 (4.9)	38 (3.2)	46 (3.4)
Discontinuation due to TEAE	19 (3.6)	9 (5.6)	54 (4.5)	63 (4.7)
Deaths	3 (0.6)	0	3 (0.3)	3 (0.2)

Deaths
Overall Safety Population

Patient	Cause of Death	Study day	Pertinent history
Placebo (0.6% patients)			
56/F	Unknown Cause of Sudden Death	15	Osteoarthritis, depression, dyslipidemia, smoking; BMI 32
58/M	Motorcycle accident	137	HTN, CABG, hyperlipidemia, DM, diabetic neuropathy, kidney stones
46/M	Sudden Cardiac Death	49	Obese with plaques in coronary arteries, fatty liver consistent with chronic ethanol use
Rilonacept 160 mg (0.2% patients)			
39/M	Myocardial Infarction	133	HTN, obese, depression, anxiety, hyperlipidemia; enlarged heart and coronary artery disease
72/M	Cerebrovascular accident	98	HTN, hypothyroidism, NIDDM, ischemic heart disease; two strokes 12 days apart
60/M	Myocardial Infarction	85	HTN; admitted to ER with peptic ulcer disease symptoms and coffee grounds emesis; Discharged and died shortly thereafter.

Discontinuations Due to Adverse Events (2 or More Patients in Any Group)

Overall Safety Population

Discontinuations due to:	Patients, n (%)			
	Placebo N=533)	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 TEAE	**19 (3.6)**	**9 (5.6)**	**54 (4.5)**	**63 (4.7)**
Injection site reactions	0	2 (1.2)	14 (1.2)	16 (1.2)
Rash	1 (0.2)	1 (0.6)	4 (0.3)	5 (0.4)
Drug eruption	0	0	2 (0.2)	2 (0.1)
Arthralgia	2 (0.4)	0	2 (0.2)	2 (0.1)
Back Pain	0	0	2 (0.2)	2 (0.1)
Headache	0	0	2 (0.2)	2 (0.1)
Accidental Overdose	1 (0.2)	0	2 (0.2)	2 (0.1)
Prostate cancer	0	0	2 (0.2)	2 (0.1)
Gout	2 (0.4)	1 (0.6)	1 (<0.1)	2 (0.1)

Treatment Emergent Adverse Events (≥ 3% in Any Group)

Overall Safety Population

System organ class MedDRA preferred term	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 TEAE	**318 (60)**	**105 (65)**	**786 (66)**	**891 (66)**
Infections and Infestations	**111 (21)**	**38 (24)**	**241 (20)**	**279 (21)**
Nasopharyngitis	16 (3)	4 (3)	49 (4)	53 (4)
Influenza	18 (3)	6 (4)	47 (4)	53 (4)
Upper respiratory tract infection	21 (4)	7 (4)	35 (3)	42 (3)
Musculoskeletal and Connective Tissue Disorders	**105 (20)**	**35 (22)**	**236 (20)**	**271 (20)**
Arthralgia	29 (5)	6 (4)	73 (6)	79 (6)
Pain in extremity	21 (4)	4 (3)	57 (5)	61 (5)
Back pain	18 (3)	4 (3)	50 (4)	54 (4)
General Disorders and Administration Site Conditions	**42 (8)**	**20 (12)**	**229 (19)**	**249 (18)**
Injection site reactions (HLT)	14 (3)	17 (11)	185 (16)	202 (15)
Nervous System Disorders	**53 (10)**	**18 (11)**	**135 (11)**	**153 (11)**
Headache	30 (6)	10 (6)	93 (8)	103 (8)
Skin and Subcutaneous Tissue Disorders	**33 (6)**	**11 (7)**	**78 (7)**	**89 (7)**
Rash	11 (2)	6 (4)	27 (2)	33 (2)
Vascular Disorders	**16 (3)**	**7 (4)**	**34 (3)**	**41 (3)**
Hypertension	14 (3)	6 (4)	31 (3)	37 (3)

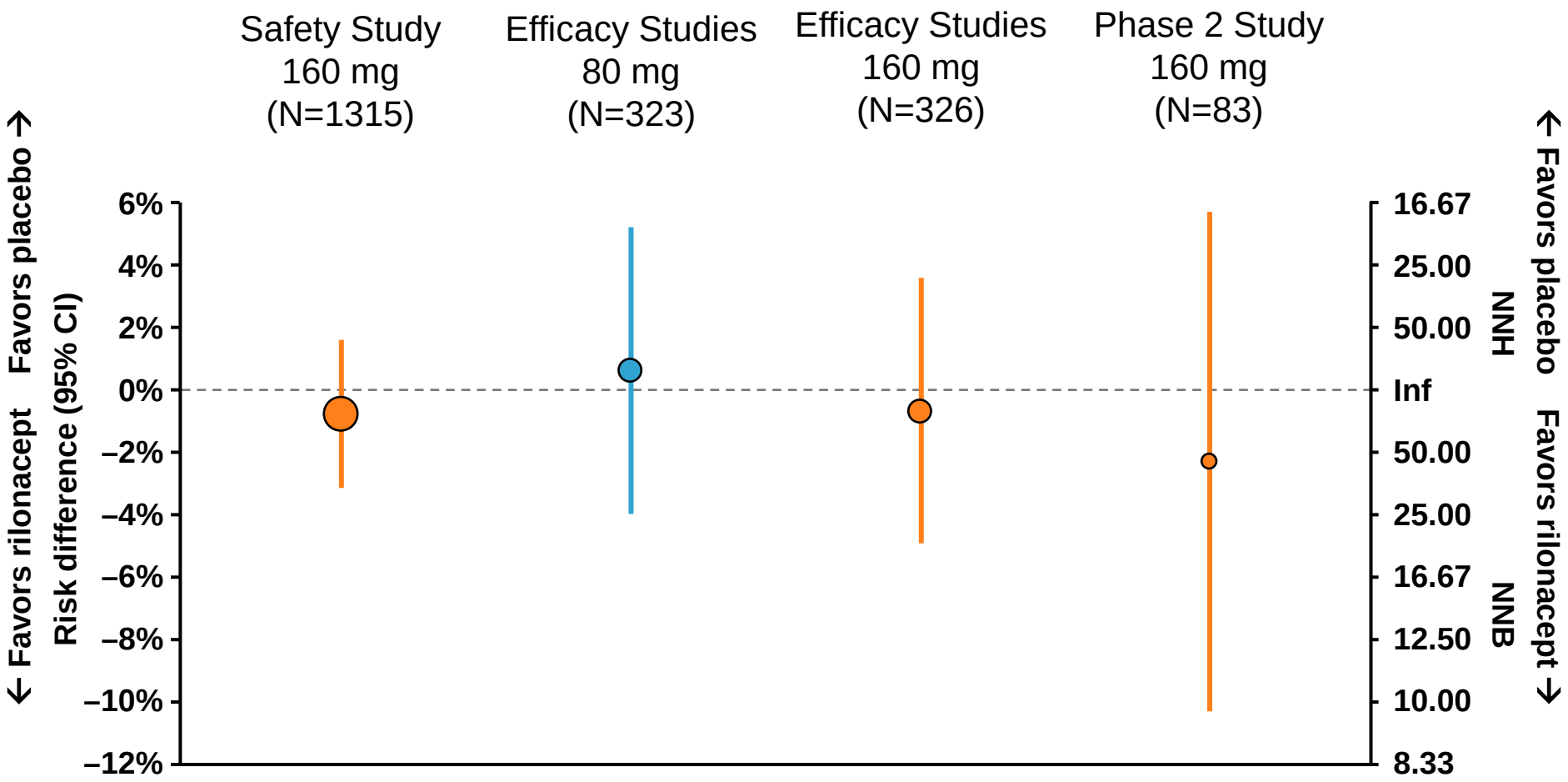
Subgroup Analyses

- **Safety of rilonacept compared to placebo not different in prespecified subgroups, including:**
  - **Age**
  - **Gender**
  - **Race**
  - **Renal function**

Safety Topics of Special Interest

- Serious AEs
  - CV Events
  - Neoplasms
- Infections
- Laboratory data
- Anti-rilonacept antibodies

Differences by Study and Dose in Incidence of Any Serious TEAE



Serious TEAEs by SOC
(2 or more patients in any group)
Overall Safety Population

System organ class	Patients, n (%)			
	Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 serious TEAE	22 (4.1)	8 (4.9)	38 (3.2)	46 (3.4)
Cardiac Disorders	1 (0.2)	0	8 (0.7)	8 (0.6)
Gastrointestinal Disorders	3 (0.6)	1 (0.6)	6 (0.5)	7 (0.5)
Infections and Infestations	3 (0.6)	3 (1.9)	5 (0.4)	8 (0.6)
Neoplasms	0	2 (1.2)	5 (0.4)	7 (0.5)
Nervous System Disorders	1 (0.2)	1 (0.6)	4 (0.3)	5 (0.4)
Metabolism and Nutrition	2 (0.4)	0	3 (0.3)	3 (0.2)
Vascular Disorders	2 (0.4)	0	3 (0.3)	3 (0.2)
General	3 (0.6)	0	1 (<0.1)	1 (<0.1)
Injury, Poisoning etc	4 (0.8)	1 (0.6)	1 (<0.1)	2 (0.1)
Psychiatric Disorders	2 (0.4)	0	1 (<0.1)	1 (<0.1)

Serious TEAEs by SOC
(2 or more patients in any group)
Overall Safety Population

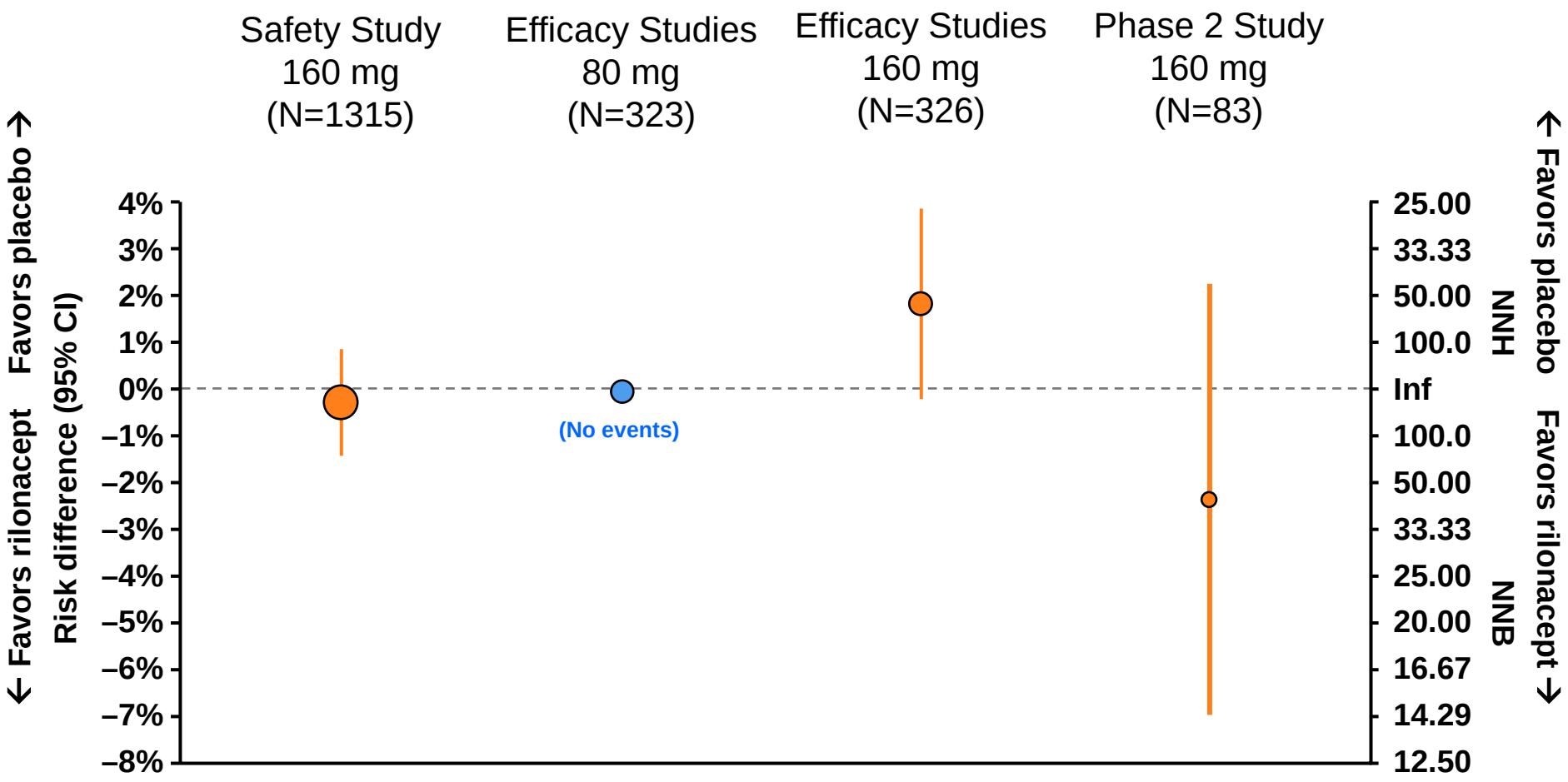
System organ class	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 serious TEAE	22 (4.1)	8 (4.9)	38 (3.2)	46 (3.4)
Cardiac Disorders	1 (0.2)	0	8 (0.7)	8 (0.6)
Gastrointestinal Disorders	3 (0.6)	1 (0.6)	6 (0.5)	7 (0.5)
Infections and Infestations	3 (0.6)	3 (1.9)	5 (0.4)	8 (0.6)
Neoplasms	0	2 (1.2)	5 (0.4)	7 (0.5)
Nervous System Disorders	1 (0.2)	1 (0.6)	4 (0.3)	5 (0.4)
Metabolism and Nutrition	2 (0.4)	0	3 (0.3)	3 (0.2)
Vascular Disorders	2 (0.4)	0	3 (0.3)	3 (0.2)
General	3 (0.6)	0	1 (<0.1)	1 (<0.1)
Injury, Poisoning etc	4 (0.8)	1 (0.6)	1 (<0.1)	2 (0.1)
Psychiatric Disorders	2 (0.4)	0	1 (<0.1)	1 (<0.1)

Treatment Emergent Cardiac and General Serious Adverse Events

Overall Safety Population

System organ class MedDRA preferred term	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
Cardiac Disorders SAEs	1 (0.2)	0	8 (0.7)	8 (0.6)
Atrial fibrillation	0	0	2 (0.2)	2 (0.1)
Myocardial infarction	0	0	2 (0.2)	2 (0.1)
Acute coronary syndrome	1 (0.2)	0	1 (<0.1)	1 (<0.1)
Cardiac failure	0	0	1 (<0.1)	1 (<0.1)
Coronary artery disease	0	0	1 (<0.1)	1 (<0.1)
Cor pulmonale	0	0	1 (<0.1)	1 (<0.1)
General Disorders SAEs	3 (0.6)	0	1 (<0.1)	1 (<0.1)
Pyrexia	0	0	1 (<0.1)	1 (<0.1)
Cyst	1 (0.2)	0	0	0
Chest Pain	1 (0.2)	0	0	0
Death	1 (0.2)	0	0	0

Differences by Study and Dose in Incidence of Serious TEAE in Cardiac or General Disorders SOC



APTC Classification Process

- Events classified using APTC combined endpoint:
  - Nonfatal myocardial infarction
  - Nonfatal stroke (ischemic or hemorrhagic)
  - Death (due to vascular or unknown causes)
- Performed by head of cardiovascular medicine at Regeneron and reviewed by external cardiologist
  - All fatal SAEs and all cardiac, vascular, and neurovascular SAEs assessed
  - Categorized as APTC event or not

Antiplatelet Trialists' Collaboration (APTC) Events

Overall Safety Population

APTC cardiovascular event Preferred term	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 APTC AE	**4 (0.8)**	**0**	**4 (0.3)**	**4 (0.3)**
≥1 APTC TEAE	**3 (0.6)**	**0**	**3 (0.3)**	**3 (0.2)**
Vascular death	**2 (0.4)**	**0**	**3 (0.3)**	**3 (0.2)**
Myocardial infarction	0	0	2 (0.2)	2 (0.1)
Cerebrovascular accident	0	0	1 (<0.1)	1 (<0.1)
Death	1 (0.2)	0	0	0
Sudden cardiac death[a]	1 (0.2)	0	0	0
Nonfatal myocardial infarction	**1 (0.2)**	**0**	**1 (<0.1)**	**1 (<0.1)**
Acute myocardial infarction[a]	0	0	1 (<0.1)	1 (<0.1)
Acute coronary syndrome	1 (0.2)	0	0	0
Nonfatal stroke	**1 (0.2)**	**0**	**0**	**0**
Cerebrovascular accident	1 (0.2)	0	0	0

[a] AE occurred 48 days after last dose.

Conclusion: Serious Cardiac AEs

- **Similar incidence of serious cardiac AEs in patients taking rilonacept versus placebo**

Safety Topics of Special Interest

- Serious AEs
  - CV Events
  - Neoplasms
- Infections
- Laboratory data
- Anti-rilonacept antibodies

Malignancy: IL-1 Blockade Not Associated With Increased Cancer Risk

- **Preclinical data and human genetic evidence indicate that blocking IL-1 decreases tumor incidence**
  - **IL-1 knock out mice develop fewer tumors[1]**
  - **Contrasting with cytokines involved in tumor immunosurveillance such as IFN gamma and IL-12[2]**
  - **Human genetic evidence focusing on polymorphisms associated with higher IL-1 expression/activity indicate higher cancer risk[3]**

1) Krelin *et al*., 2007. *Cancer Res.* **67**:1062-1071
2) Noguchi *et al*., 1996. *Proc. Natl. Acad. Sci. USA*. **93**:11798-11801 and 2 others
3) Barber *et al*., 2000. *Br J Cancer.* 83:1443-7 and 5 others

Serious TEAEs by SOC
(2 or more patients in any group)
Overall Safety Population

System organ class	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
≥1 serious TEAE	22 (4.1)	8 (4.9)	38 (3.2)	46 (3.4)
Cardiac Disorders	1 (0.2)	0	8 (0.7)	8 (0.6)
Gastrointestinal Disorders	3 (0.6)	1 (0.6)	6 (0.5)	7 (0.5)
Infections and Infestations	3 (0.6)	3 (1.9)	5 (0.4)	8 (0.6)
Neoplasms	0	2 (1.2)	5 (0.4)	7 (0.5)
Nervous System Disorders	1 (0.2)	1 (0.6)	4 (0.3)	5 (0.4)
Metabolism and Nutrition	2 (0.4)	0	3 (0.3)	3 (0.2)
Vascular Disorders	2 (0.4)	0	3 (0.3)	3 (0.2)
General	3 (0.6)	0	1 (<0.1)	1 (<0.1)
Injury, Poisoning etc	4 (0.8)	1 (0.6)	1 (<0.1)	2 (0.1)
Psychiatric Disorders	2 (0.4)	0	1 (<0.1)	1 (<0.1)

All Malignant Neoplasms
Overall Safety Population

System organ class	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
Neoplasms	1 (0.2)[a]	2 (1.2)[b]	5 (0.4)	7 (0.5)[b]

[a] Includes basal cell skin cancer

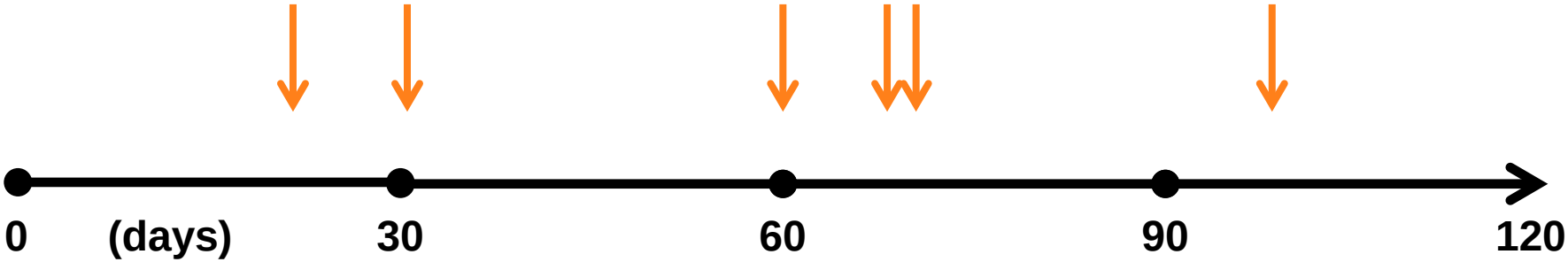
[b] Includes squamous cell skin cancer (date of onset unclear)

Neoplasms excluding non melanoma skin cancer

Neoplasms	0	1 (0.6)	5 (0.4)	6 (0.4)

Malignant Neoplasms – Excluding Skin Cancers: SAE Start Date[a]

Overall Safety Population



[a]Date that the investigator determined that the findings represented a serious adverse event

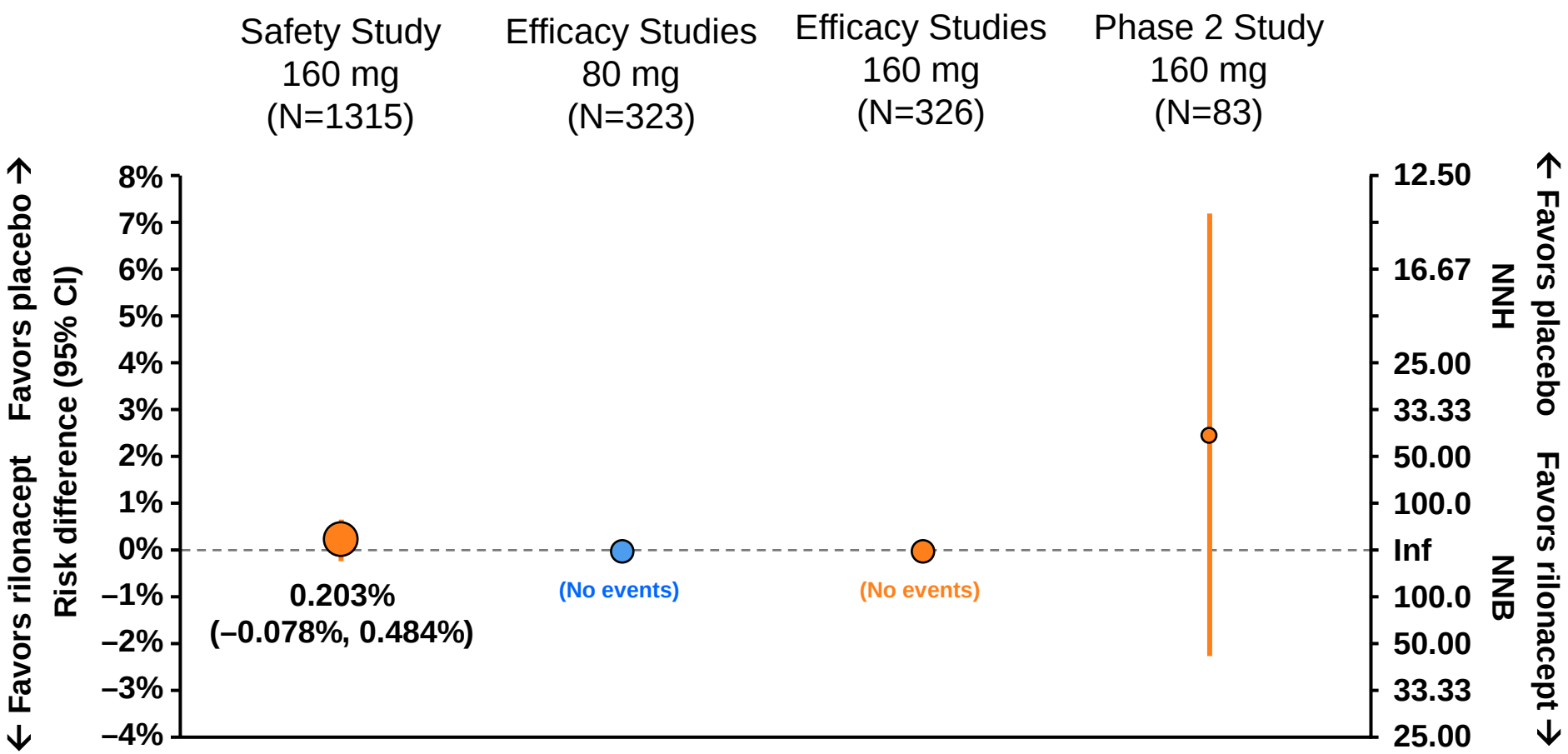
Malignant Neoplasms – Excluding Skin Cancers: Clinical Assessment

Diagnosis	Age/Sex	Onset of signs/symptoms	AE start	Assessment
Prostate cancer	71/M	Elevated PSA 69 days pre-study	Day 20 (prostatectomy)	Prior diagnosis
Gastric adenocarcinoma	70/M	Baseline anemia, rapidly progressed	Day 32 (endoscopy)	Prior evidence
Prostate cancer	56/M	Elevated PSA 17 days pre-study	Day 60 (biopsy)	Prior evidence
Ductal carcinoma in situ—R breast	72/F	Lump detected Day 70	Day 70	No prior evidence
Prostate cancer	67/M	No prior clinical detail	Day 78 (routine exam)	No prior evidence
Oropharyngeal carcinoma	52/M	Mass detected Day 103	Day 103	No prior evidence

Malignant Neoplasms – Excluding Skin Cancers: Clinical Assessment

- 3 Neoplasms in rilonacept group were diagnosed pre-study or had prior evidence of disease
- 3 Neoplasms in rilonacept group for which there was no prior evidence
  - 3 of 1353 patients (0.2%) on rilonacept versus 0 of 533 patients on placebo
  - Difference equates to single neoplasm in placebo group

Malignant Neoplasms – Excluding Skin Cancers: Statistical Assessment (Excluding Cases With Prior Diagnosis or Evidence)



Malignant Neoplasms: Epidemiologic Assessment

- **Consistent with expected number of cases based on SEER[1] data and from 2 epidemiologic studies[2,3] in patients with gout**

[1] Surveillance, Epidemiology and End-Results (SEER) database, NCI
[2] Kuo et al. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.09.011
[3] Boffetta et al. Eur J Cancer Prev (2009) 18:127

Conclusion: Malignant Neoplasms

- Clinical, statistical, and epidemiologic data do not suggest an increase of malignancy with rilonacept compared to placebo
- Preclinical data and human genetic evidence do not support a mechanism of action whereby rilonacept would increase cancer risk

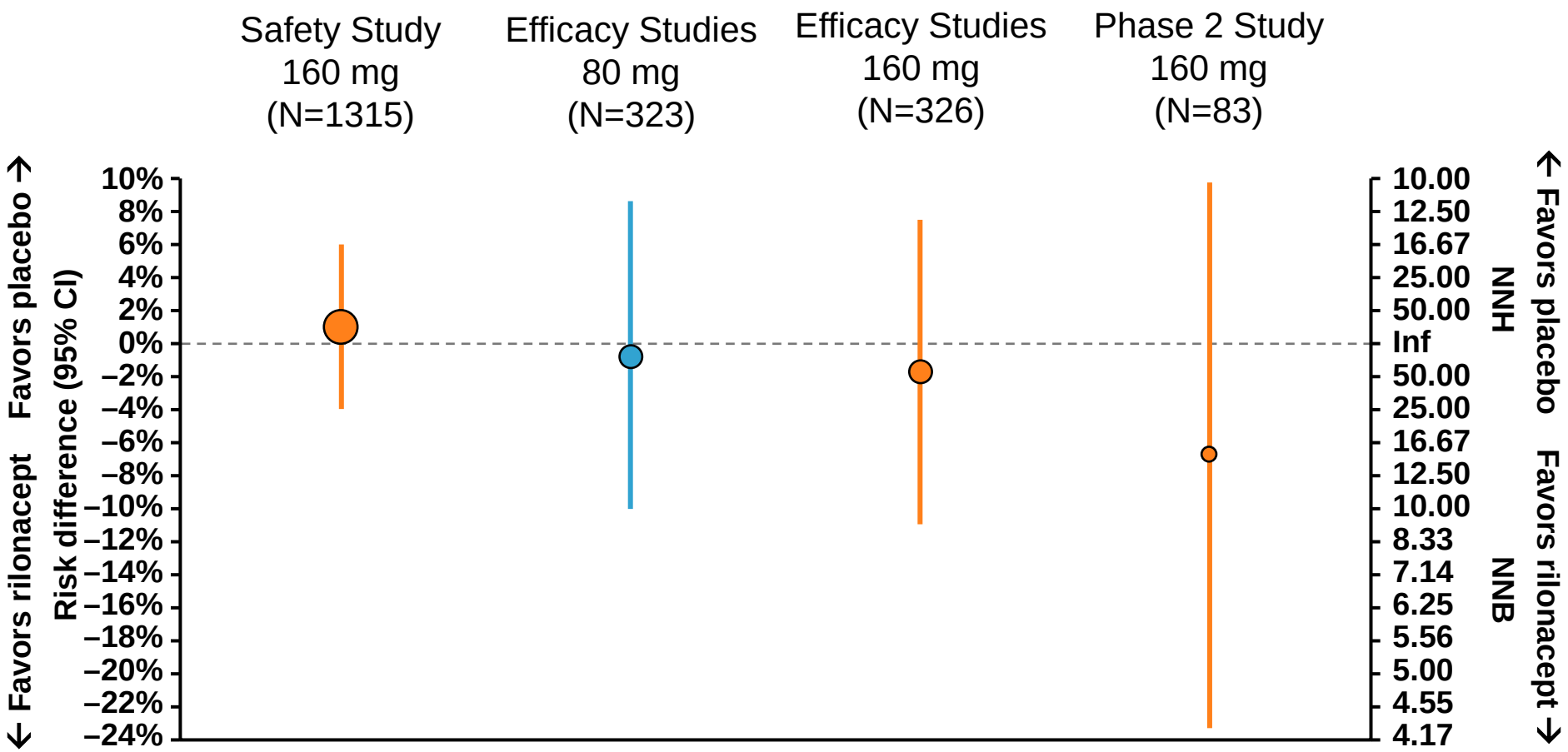
Safety Topics of Special Interest

- Serious AEs
  - CV Events
  - Neoplasms
- Infections
- Laboratory data
- Anti-rilonacept antibodies

Infection TEAEs
Overall Safety Population

	Patients, n (%)			
	Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
Any infection	**111 (20.8)**	**38 (23.5)**	**241 (20.2)**	**279 (20.6)**
Severe infection	5 (0.9)	2 (1.2)	4 (0.3)	6 (0.4)
Serious infection	3 (0.6)	3 (1.9)	5 (0.4)	8 (0.6)

Differences by Study and Dose in Incidence of Any TEAE in Infection/ Infestations SOC

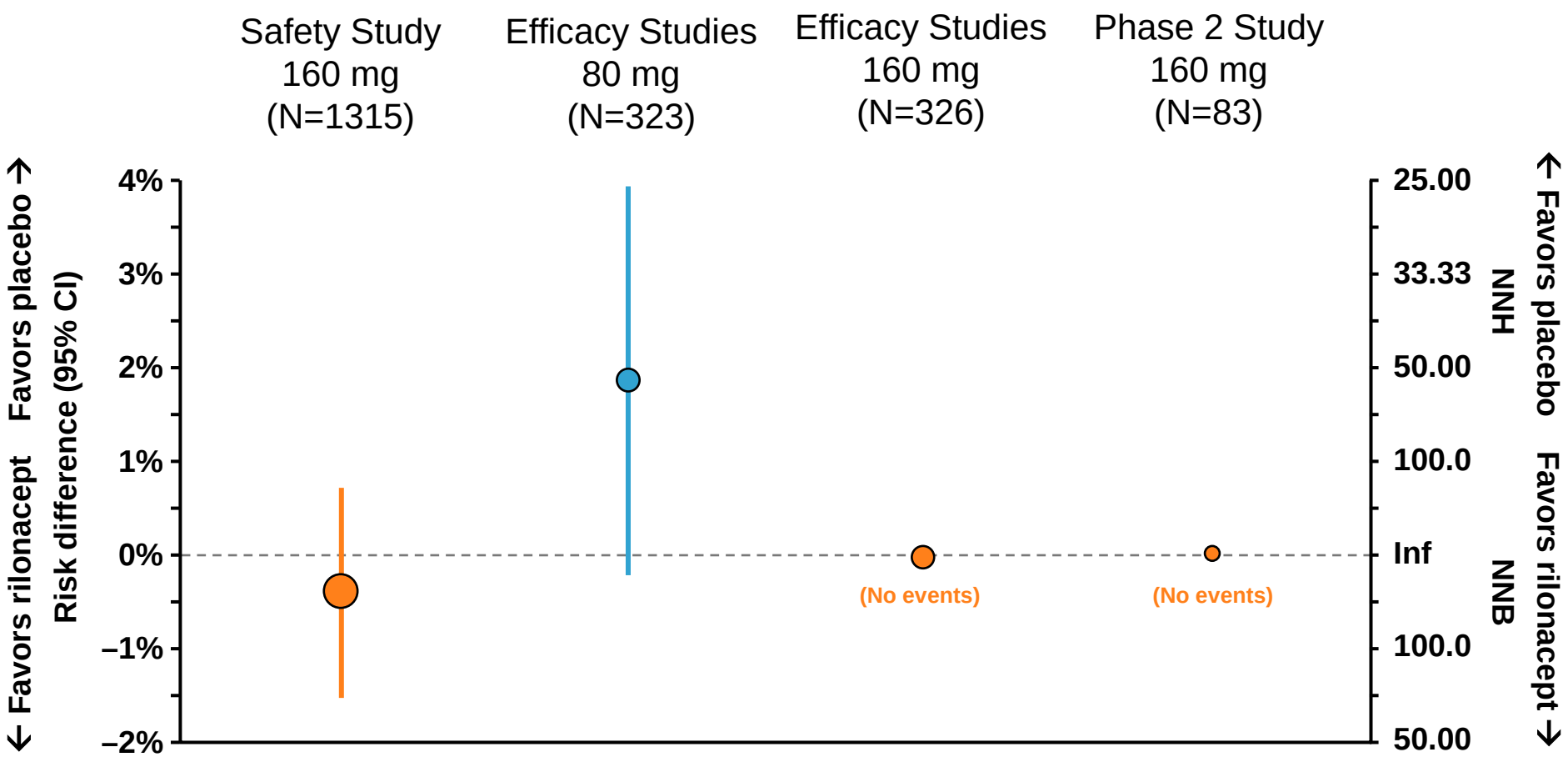


Types of Infection TEAEs ≥1.5% in Any Group – High Level Term

Overall Safety Population

System organ class MedDRA high level term	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
INFECTIONS & INFESTATIONS	**111 (20.8%)**	**38 (23.5%)**	**241 (20.2%)**	**279 (20.6%)**
Upper respiratory tract	54 (10.1%)	17 (10.5%)	123 (10.3%)	140 (10.3%)
Influenza viral	18 (3.4%)	6 (3.7%)	47 (3.9%)	53 (3.9%)
Urinary tract	5 (0.9%)	1 (0.6%)	20 (1.7%)	21 (1.6%)
Lower respiratory tract & lung	8 (1.5%)	4 (2.5%)	16 (1.3%)	20 (1.5%)
Abdominal & gastrointestinal	3 (0.6%)	3 (1.9%)	11 (0.9%)	14 (1.0%)
Viral NEC	6 (1.1%)	3 (1.9%)	11 (0.9%)	14 (1.0%)
Ear	1 (0.2%)	3 (1.9%)	10 (0.8%)	13 (1.0%)
Bacterial NEC	9 (1.7%)	1 (0.6%)	7 (0.6%)	8 (0.6%)
Dental & oral soft tissue	2 (0.4%)	3 (1.9%)	5 (0.4%)	8 (0.6%)

Differences by Study and Dose in Incidence of Any Serious TEAE in Infections/Infestations SOC



Serious Infection TEAEs
Overall Safety Population

System organ class MedDRA preferred term	Patients, n (%) Placebo N=533	Rilonacept 80 mg N=162	Rilonacept 160 mg N=1191	All rilonacept doses N=1353
Infections and Infestations	**3 (0.6)**	**3 (1.9)**	**5 (0.4)**	**8 (0.6)**
Arthritis bacterial	0	0	1 (<0.1)	1 (<0.1)
Bronchitis	0	0	1 (<0.1)	1 (<0.1)
Cellulitis	2 (0.4)	0	1 (<0.1)	1 (<0.1)
Diverticulitis	0	0	1 (<0.1)	1 (<0.1)
Sepsis	0	0	1 (<0.1)	1 (<0.1)
Urinary tract infection	0	0	1 (<0.1)	1 (<0.1)
Appendicitis	0	1 (0.6)	0	1 (<0.1)
Liver abscess	0	1 (0.6)	0	1 (<0.1)
Meningitis viral	1 (0.2)	0	0	0
Pyelonephritis	0	1 (0.6)	0	1 (<0.1)

Conclusion: Infections

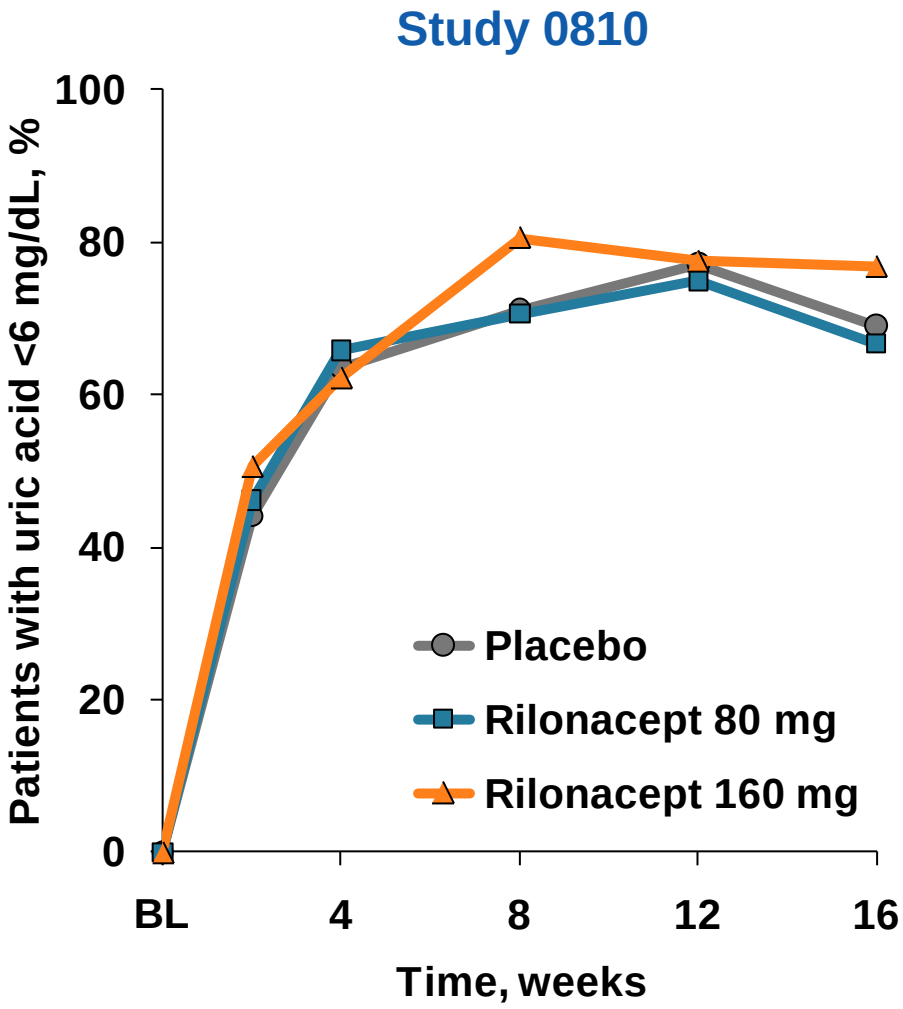
- **Similar incidence of infections, including serious infections, in patients taking rilonacept versus placebo**

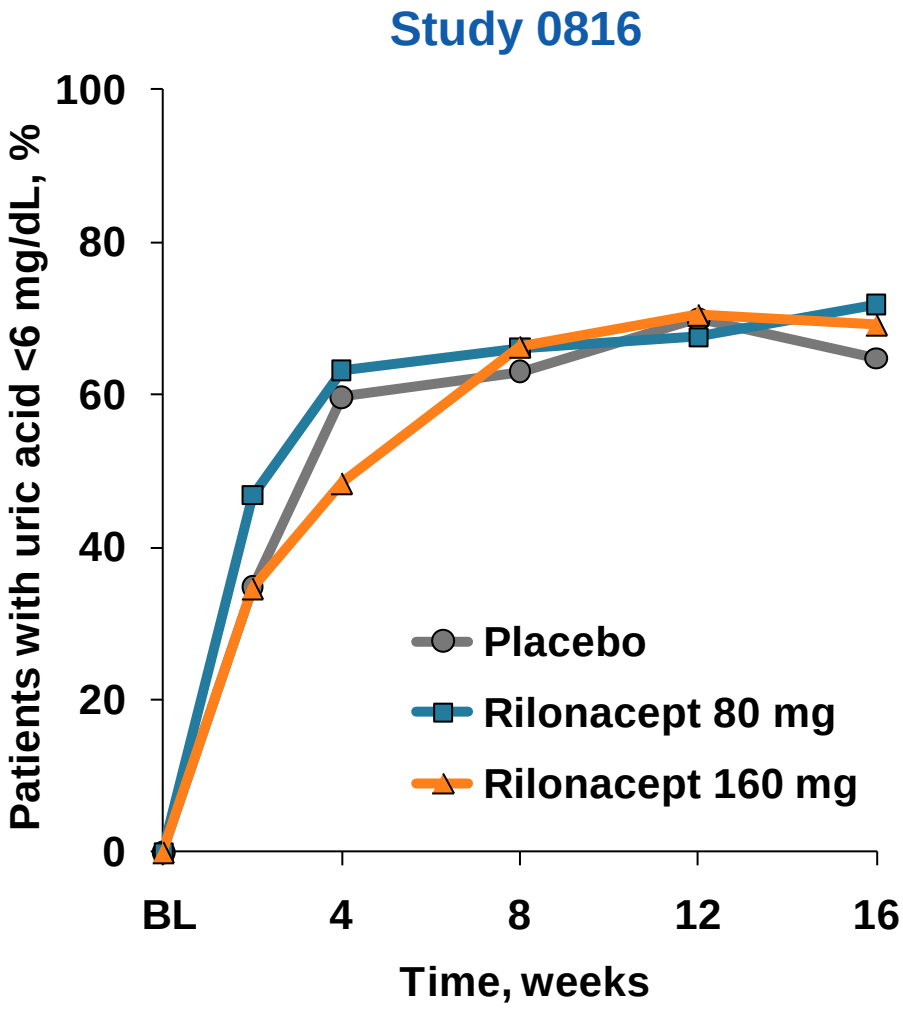
Laboratory Data

- Changes consistent with our understanding of IL-1 blockade
  - Neutrophils
- No effect on uric acid

Proportion of Patients Achieving Uric Acid Target <6 mg/dL by Visit

Confirmatory Efficacy Studies 0810 and 0816





Anti-Rilonacept Antibodies

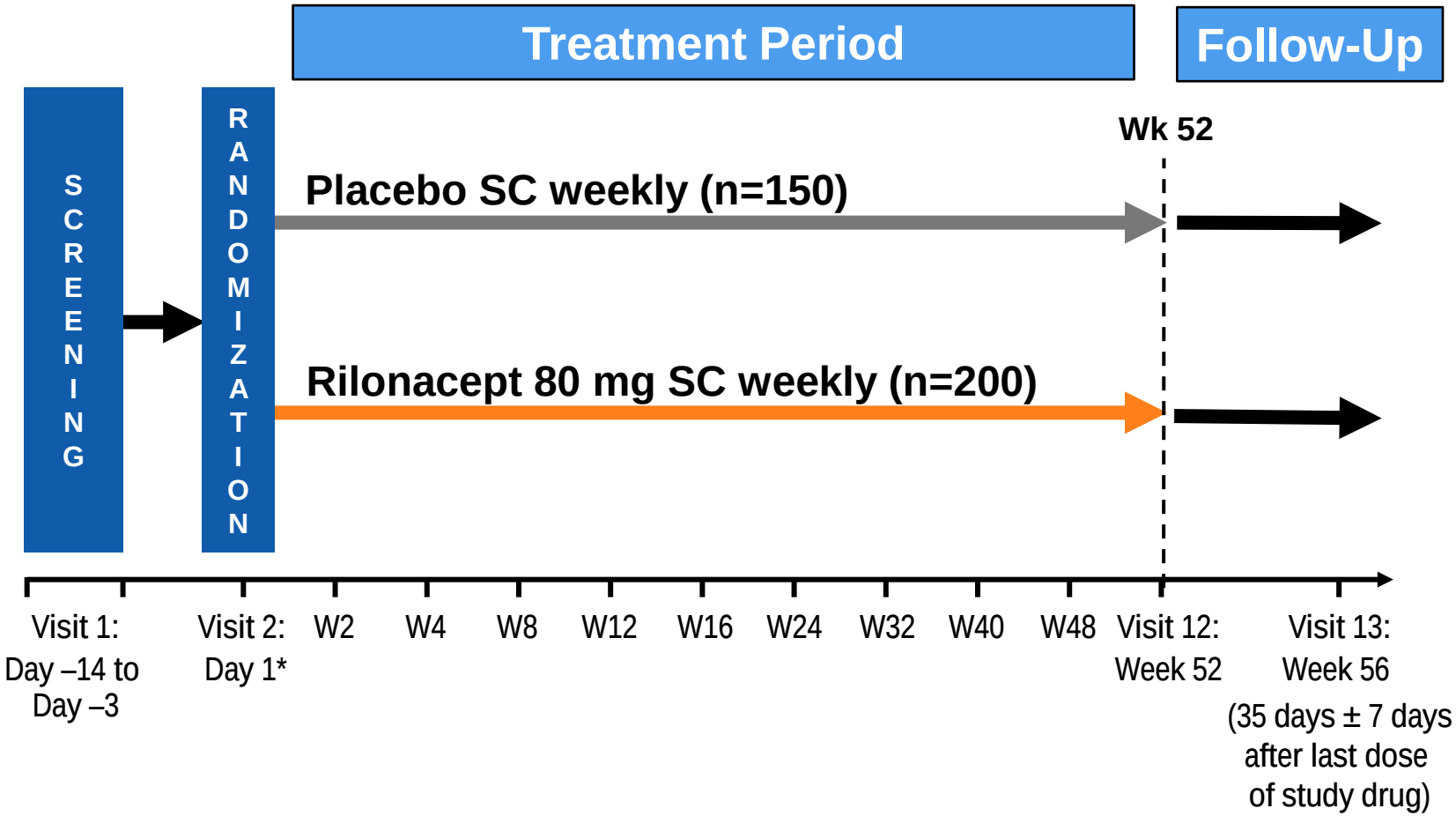
- 407 (30.1%) of 1353 patients positive for anti-rilonacept antibodies
- 7.2% of all patients had neutralizing antibodies
- Other than ISRs, did not affect efficacy or safety profile

Risk Management Plan

Postmarketing Activities

- Encourage 16-week-only use
  - Labeling
  - Physician education
- Capture data on longer use
  - Specialty pharmacy
  - Mandatory registry for gout patients prescribed rilonacept > 16 weeks
- Ongoing 1-year safety study: (N=350)

Study Design
One Year Safety Study 1101



***Double dose of study drug and initiate allopurinol 300 mg daily on Day 1 (all groups); titrate to achieve serum urate levels <6 mg/dL**

Benefit Risk Conclusions

Benefit Summary

- Rilonacept significantly reduced gout flares compared to placebo in patients initiating ULT
  - Demonstrated efficacy at 16 weeks in primary and all secondary endpoints
- Rilonacept 80 and 160 mg were consistently superior to placebo
- Rilonacept was effective across subgroups
  - Including patients with greater burden of disease for whom clinicians might prescribe this treatment
- A 16-week course of treatment with rilonacept appears sufficient to eliminate the excess flares associated with initiating uric-acid lowering therapy

Safety Summary (1)

- Dose-related increase in frequency and severity of ISRs with rilonacept
  - Mostly mild to moderate and infrequently led to discontinuation of study therapy
- No increased rate of cardiac events vs placebo
- Small numeric imbalance in neoplasms does not appear to be treatment related
  - Preclinical data do not support that IL-1 blockade increases risk of malignancy

Safety Summary (2)

- No increased rate or severity of infection
- Laboratory data only notable for <1% patients with neutropenia
  - Quickly resolves without increased infections
- Anti-rilonacept antibodies did not affect efficacy or safety
- Encourage 16-week-only use
  - Capture data on longer use via registry
- A 1-year safety study is ongoing (N=350)

Overall, benefits outweigh the risks of rilonacept use in the proposed setting

Clinical Perspective

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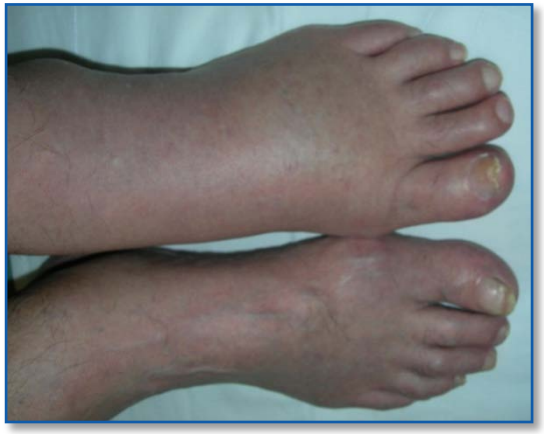
Clinical Scenarios Requiring Alternative Prophylaxis Therapies in Gout

- **Co-morbid conditions**
  - CKD
  - DM
  - CHF
  - Obesity
  - GERD
  - Gastric ulcers
- **Intolerance to standard therapies**
  - NSAIDs
  - Colchicine
  - Glucocorticoids
- **Difficult to manage with standard therapies**
  - Advanced disease
    - Polyarticular
    - Tophi
  - Aggressive ULT

Case Study 1: Initiating Urate-Lowering Therapy in Patient with Acute Intermittent Gout

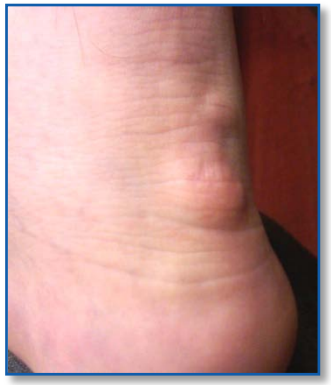
- 71 year-old retired hospital administrator
- Multiple comorbidities:
  - CAD, CHF, CKD, HTN, Type-2 DM,
- Medications:
  - Insulin, fenofibrate, ACEi, ASA, simvastatin, furosemide
- 6 gouty attacks over past 3 years
- sUA 11.4 mg/dL; sCreat 2.1 mg/dL



- Hospitalized (gout and neuropathy)
  - Tx: prednisone 40 mg/day × 1 week followed by colchicine 0.6 mg/day
  - Average morning glucose increased from 125 to 190
- Post-hospitalization
  - Developed diarrhea on colchicine (6 stools/day), abdominal pain, and stopped colchicine
  - Prednisone 10 mg/day
  - Allopurinol 100 mg/day with dose escalation to 400 mg/day
  - After 4 mos sUA 5.3 mg/dL with 2 flares
  - HbA1c increased from 6.8 to 8.7 in 5 mo period

Case Study 2: Escalating Urate-Lowering Therapy in Patient with Advanced Gout

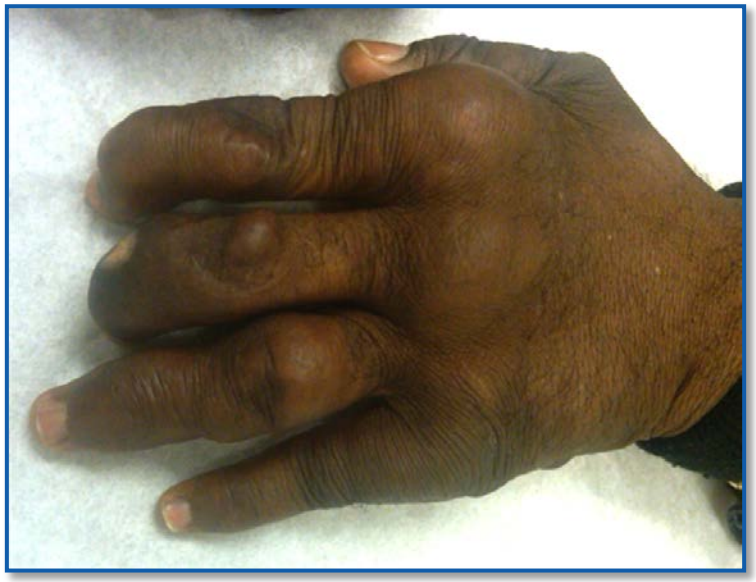
- 44 year-old construction worker
- 8-year history of gout and fatty liver disease
- Medications:
  - Allopurinol 600 mg/day, colchicine 0.6 mg BID, diclofenac; indomethacin for flares
- Tophi on right 3rd PIP joint and Achilles tendon, with erosions on radiographs
- sUA 9.5 mg/dL; sCreat 0.9 mg/dL
- AST/ALT 54/66 (with further elevations when allopurinol ↑ above 600 mg/day)
- Flares every 6-8 weeks



- Surgery for ACL tear: sUA 13.8 mg/dL
  - Severe flare right wrist
- Poor response to multiple IV and IA steroid injections: aggressive behavior
- Anakinra 100 mg SC daily × 3
- Post-hospitalization
  - Previous anti-inflammatories plus febuxostat up to 80 mg/day: sUA 7.4 mg/dL
  - Probenicid added over next 2 months with sUA to 5.8 mg/dL; rate of flares ↑ to every 4 weeks
  - Oral prednisone 20 mg/day resulted in aggression and personality changes
  - Still on work disability

Case Study 3: Advancing Urate-Lowering Therapy in Patient with Acute and Chronic Gout

- 43 year-old corrections officer
- 20-year history of gout with 1-2 flares/month
- Severe polyarticular, tophaceous gout for past 8 years
- Kidney stones, HTN, and UGI bleed from NSAIDs



- Medications:
  - Allopurinol 800 mg/day and colchicine BID; prednisone for flares
- sUA 8.8 mg/dL, creatinine 0.9 mg/dL
- Switched to febuxostat with increase in flares (every 8-10 days) during early months of therapy; sUA 5.3 mg/dL
- 10 mg prednisone/day added to colchicine BID
- Over next 4 months, 5 visits to ED for gout flare

Unmet Needs in Presented Patient Cases

- **Case Study 1**
  - **Comorbidities: DM and CKD**
  - **Intolerance: GI problems with NSAIDs and colchicine**
- **Case Study 2**
  - **Intolerance: glucocorticoids**
  - **Difficult to manage with standard therapies: NSAIDs and colchicine**
- **Case Study 3**
  - **Comorbidities: HTN**
  - **Intolerance: NSAIDs**
  - **Difficult to manage with standard therapies: colchicine and glucocorticoids**

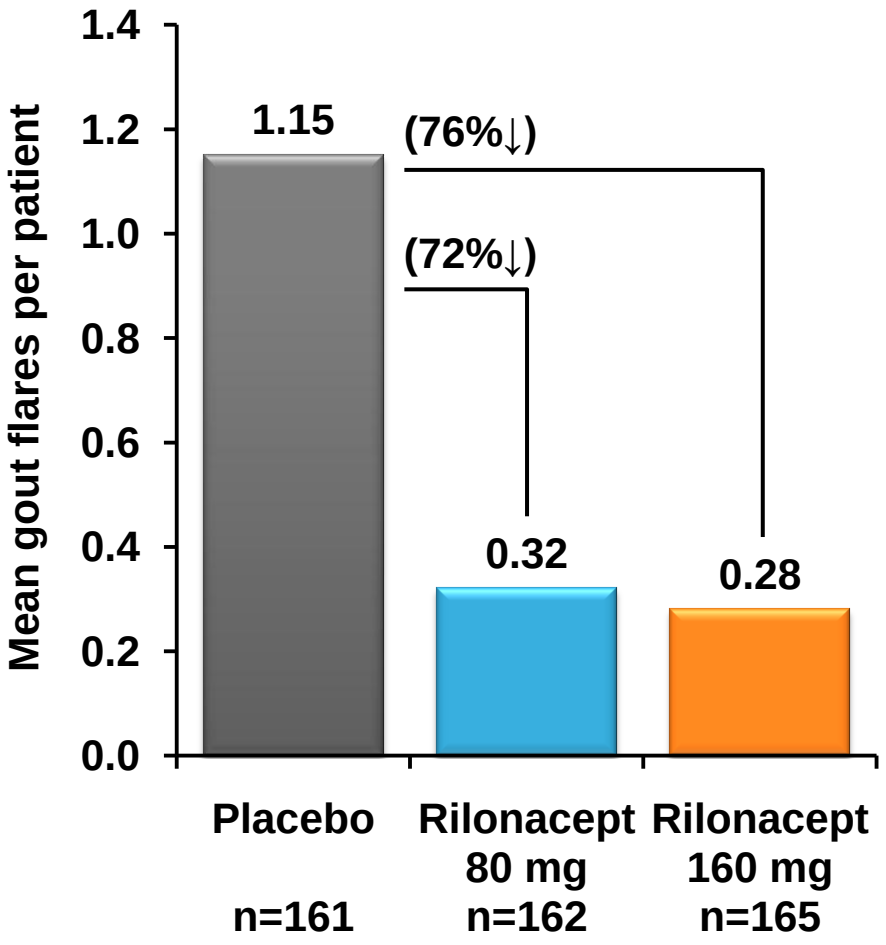
Conclusion

- ULT-associated gout flares are considered to be a major factor in patient non-compliance
- Easily demonstrable need for alternative forms of anti-inflammatory prophylaxis in gout
- I have patients for whom rilonacept would be a benefit

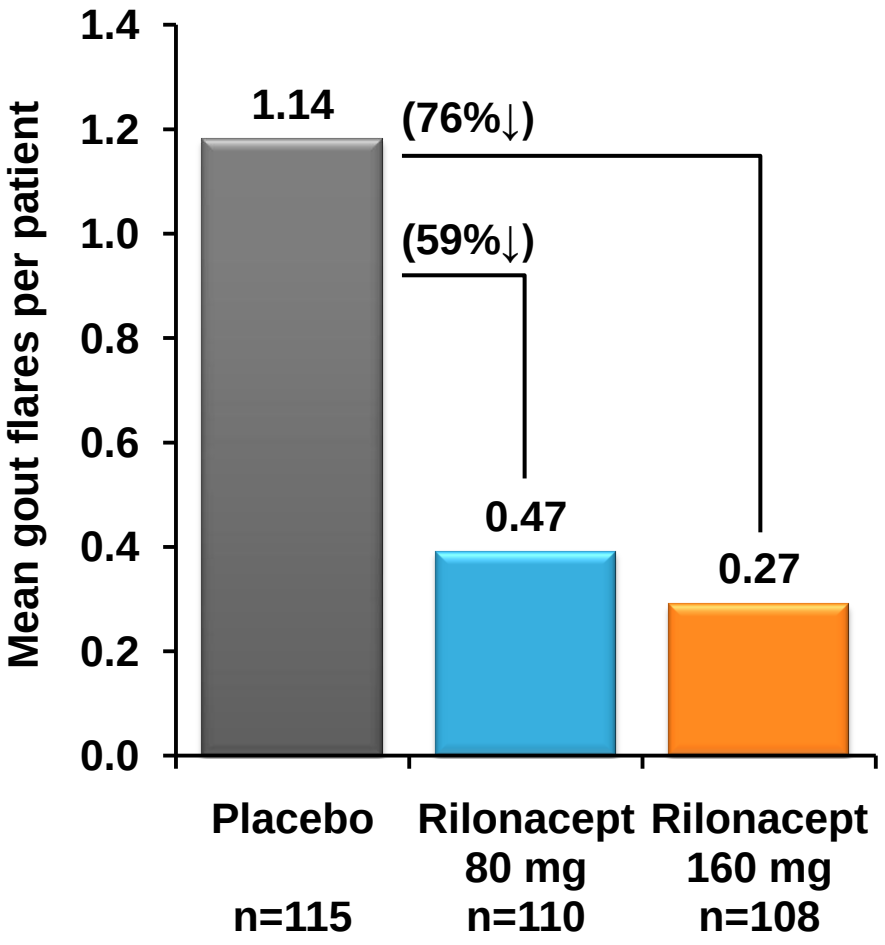
Mean Gout Flares per Patient: NSAIDs or colchicine inadvisable

Studies 0810 and 0816

General population

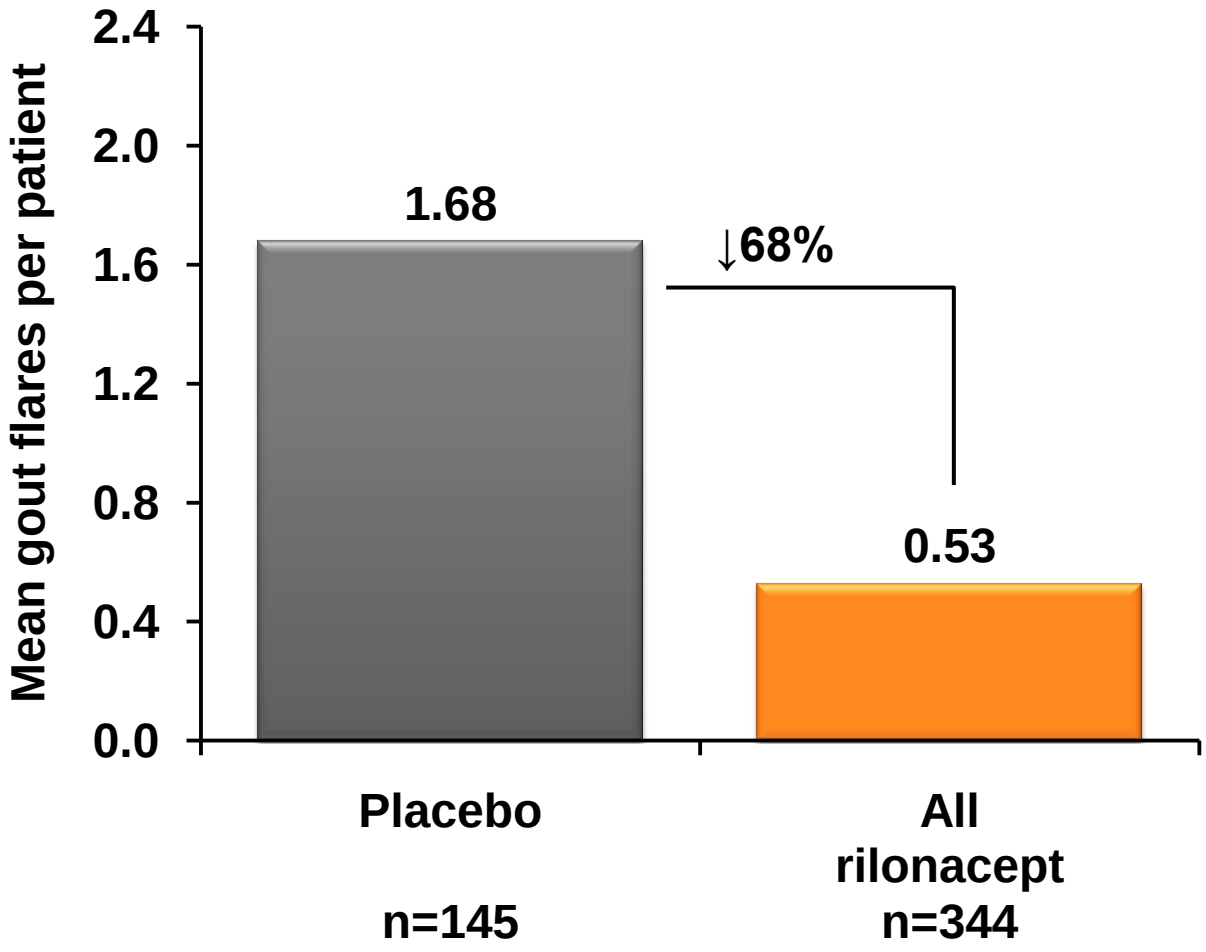


NSAIDs or colchicine inadvisable



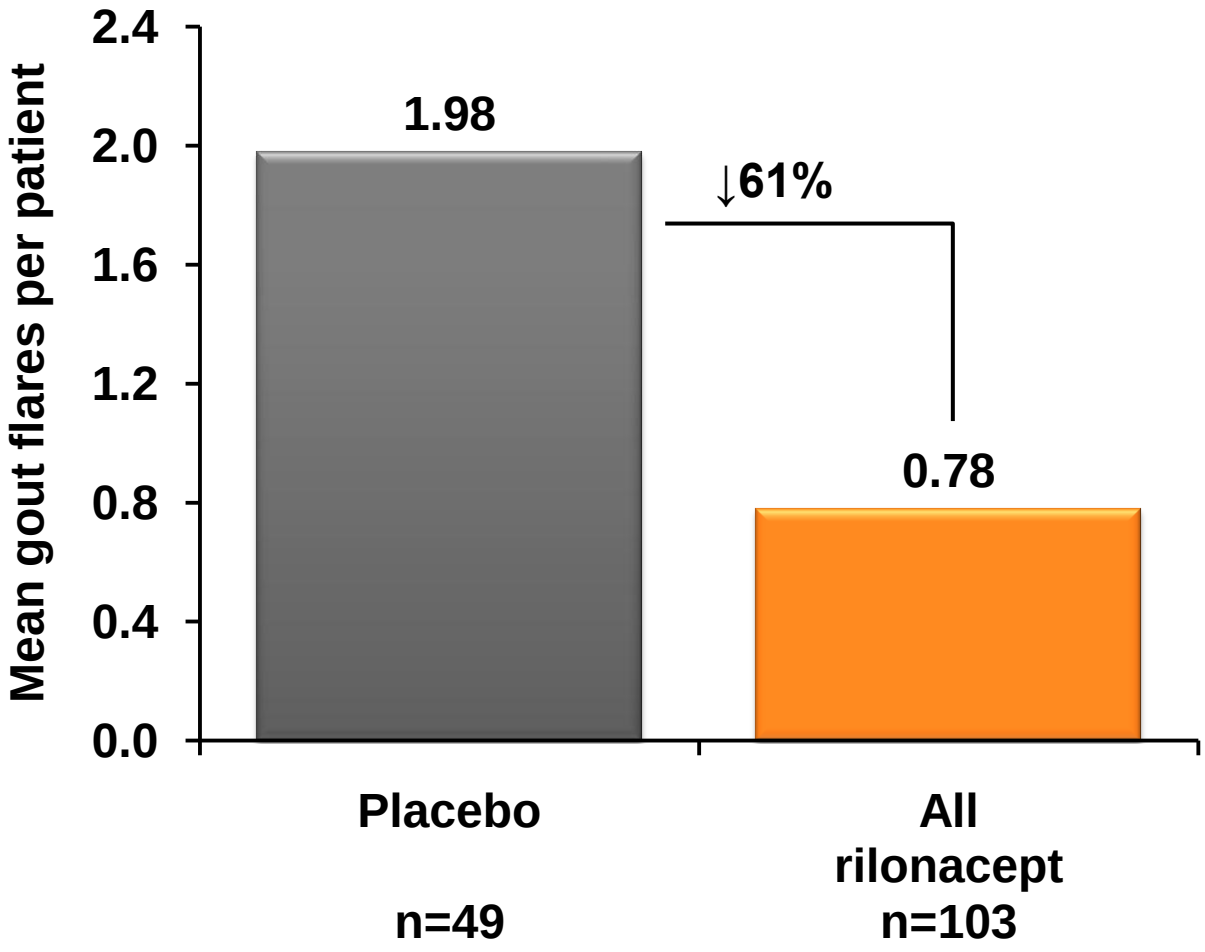
Mean Gout Flares per Patient (NSAIDs inadvisable)

Studies 0810, 0816 and 0815

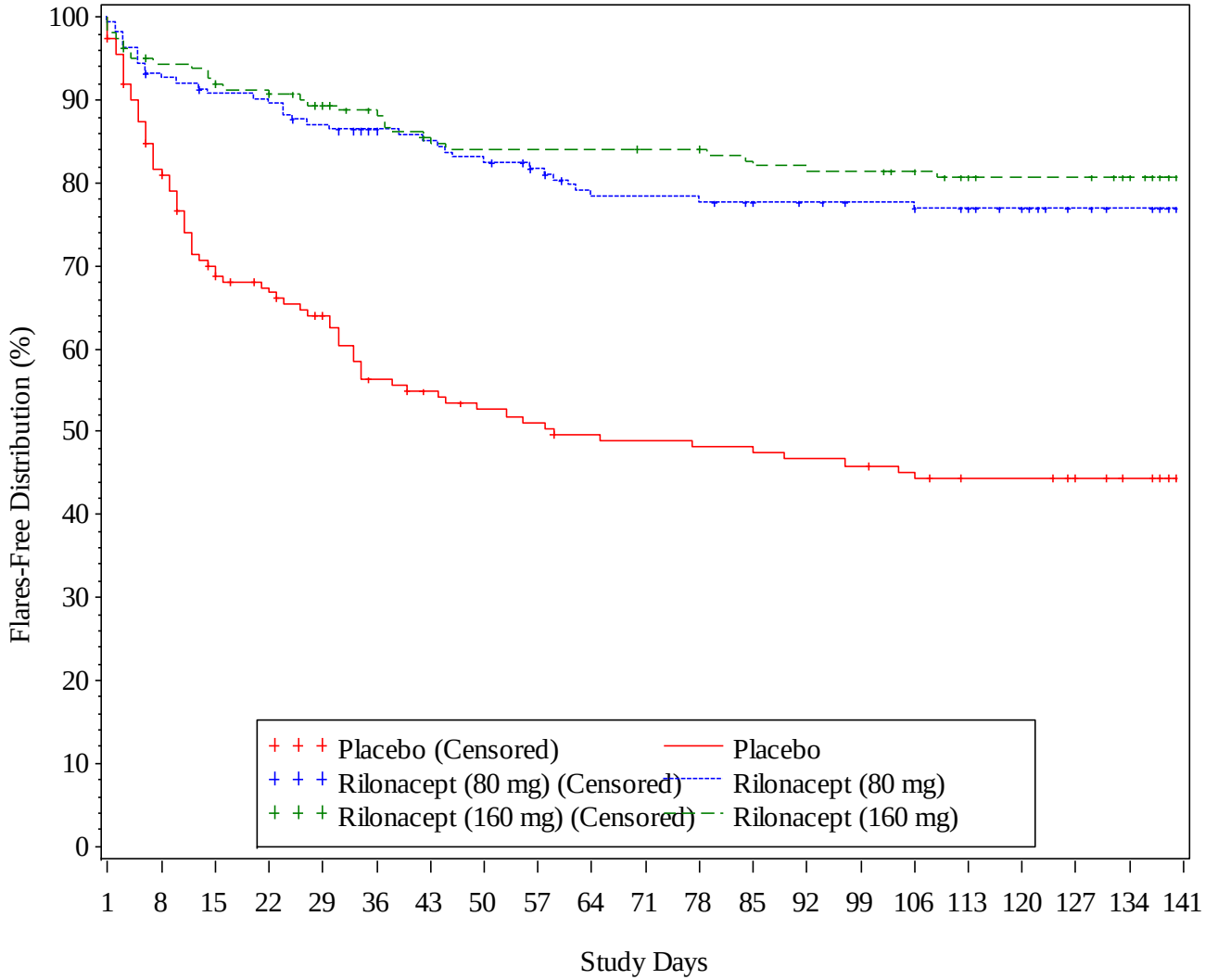


Mean Gout Flares per Patient (eGFR <60 mg/dL)

Studies 0810, 0816 and 0815



Time to First Gout Flare, Day 1 to Wk 20
Studies 0810 and 0816



Malignancies in Gout: Sources for Calculation of Expected Numbers of Cases

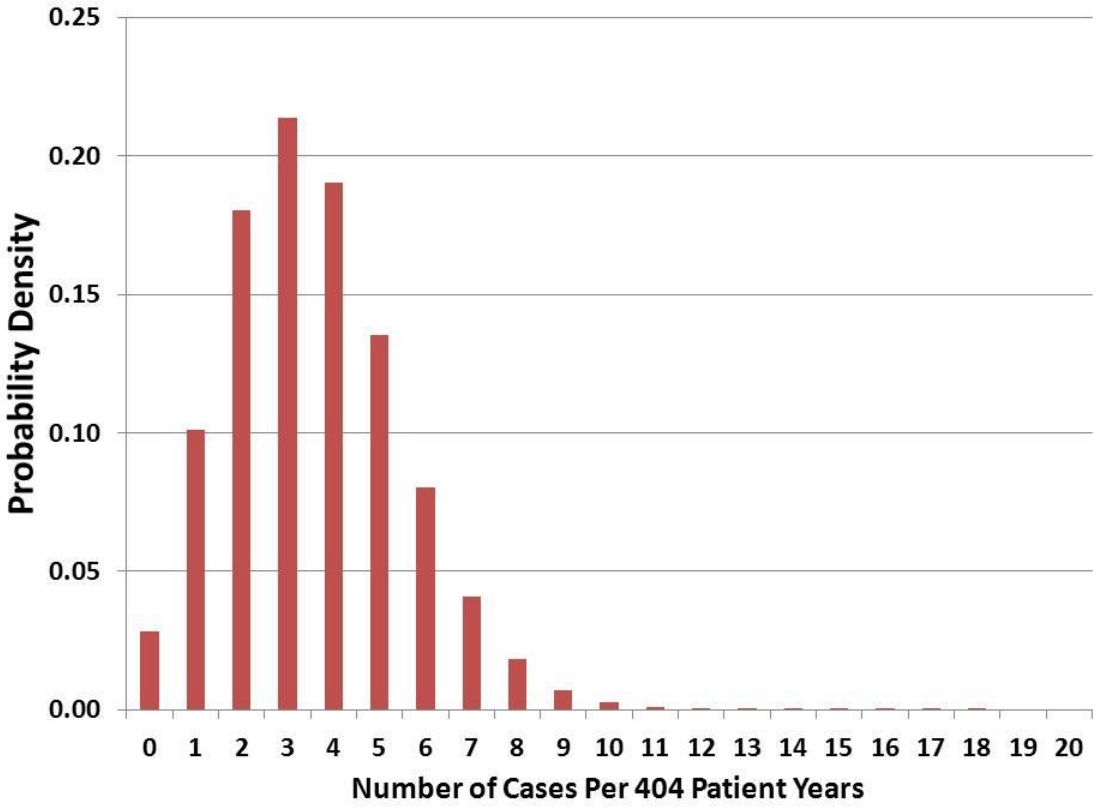
Source	Patients	Region	Comment
SEER[1]	US population	US	Excludes non-melanoma skin cancers and in situ breast cancer
Kuo et al[2]	Gout patients	Taiwan	Mean age 55
Boffetta et al[3]	Gout patients	Sweden	75% pts ≥ 65 y/o

1. Surveillance, Epidemiology, and End Results (SEER) program, NCI http://seer.cancer.gov
2. Kuo et al. Joint Bone Spine (2011), doi:10.1016/j.jbspin.2011.09.011
3. Boffetta et al. Eur J Cancer Prev (2009) 18:127

Expected malignancy rates in Rilonacept program based on SEER

- $Y = \Sigma n_i X_i$ where
  - N_i = pt-year exposure (rilonacept) in half decades of age
  - X_i = SEER rate of cancers in half decade adjusted for overall gender distribution in rilonacept program
- Poisson distribution used to determine likely range of Y values

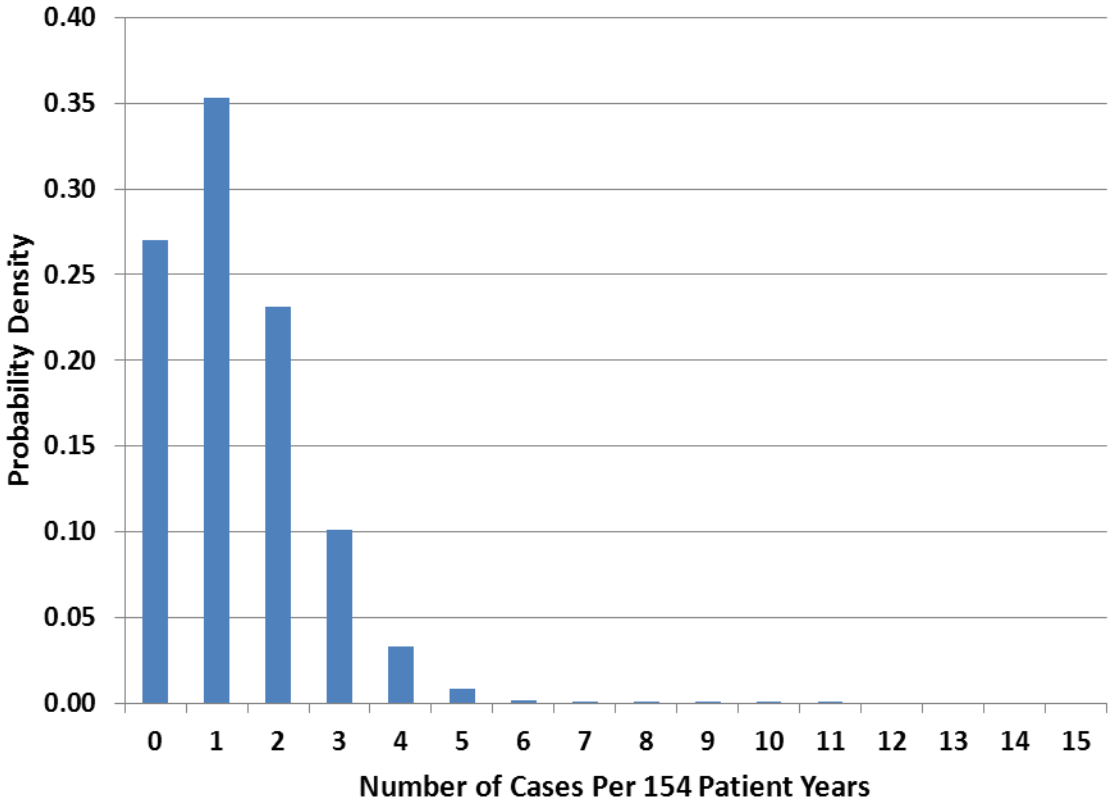
Expected malignancy rates in Rilonacept-Treated Gout Patients based on SEER: 3.56 Cancers/404 Patient Years



- **Observed: 5**
- **Observed No Prior Evidence: 2**
- **Mean = 3.56**
- **Variance = 3.56**
- **Prob (0 ≤ X ≤ 6) = 93.0%**
- **Prob (≥5) = 28.6%**

Observed Numbers of Cancers Consistent with Expected Numbers based on Poisson Distribution

Expected malignancy rates in Placebo-Treated Gout Patients based on SEER: 1.31 Cancers/154 Patient Years



- **Observed: 0**
- **Observed No Prior Evidence: 0**
- **Mean = 1.31**
- **Variance = 1.31**
- **Prob (0) = 27.0%**

Observed Numbers of Cancers Consistent with Expected Numbers based on Poisson Distribution

Expected Malignancy Rates in Rilonacept Program Based on Epidemiology Studies

	Rate per 1000 PEY	# per 404 PEYs	Comment
Kuo et al.	8.7	3.5	Taiwanese
Boffetta et al.	18.5	7.5	Swedish population older than rilonacept program

Postmarketing Exposure

- As of 14-Sep-2011:
  - 196 patients treated with rilonacept
  - 77 of these patients had been on treatment since product launch (May 2008)
  - 68 of these patients were in clinical trials using ARCALYST

Rilonacept Exposure in Other Regeneron-Sponsored Clinical Trials

Indication	# Patients Treated	Estimated Person Years
CAPS	109	148.5
Other (excluding healthy volunteers)*	406	96.1

- Other includes:
  - Rheumatoid arthritis
  - Adult Still's disease
  - Familial Mediterranean fever
  - Polymyalgia rheumatic
  - Osteoarthritis
  - Coronary artery disease
  - Systemic juvenile idiopathic arthritis
  - End stage renal disease

Other Malignancies in Rilonacept Safety Database

Age/ Gender	Indication	Malignancy	Rilonacept Exposure Prior to Diagnosis	Comment
Clinical Studies				
68/F	Rheumatoid Arthritis	Non-small cell lung cancer	6 doses	47 year smoking history
52/F	Rheumatoid Arthritis	Lung adenocarcinoma	3 doses	25 year smoking history
55/M	Still's disease	Prostate cancer	Over 2.5 years	Continued rilonacept use through cancer treatment
Postmarketing				
73/M	FCAS	Lung cancer	Less than 3 months	60 year smoking history

Loading Dose Reduces the Time to Therapeutic/Target Systemic Concentrations